STAPHYLOCOCCAL SEPTICÆMIA

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IN recent years increasing attention has been paid to the problem of staphylococcal cross-infection in hospitals. This has been due partly to an increase in the incidence of neonatal infection in maternity hospitals but also to growing appreciation of the dangers attending cross-infection with antibiotic-resistant staphylococci in patients undergoing surgery (Howe 1954, Spink 1954, Barber and Burston 1955, Blowers et al. 1955, Wysham and Kirby 1957).

In this large hospital, generalised staphylococcal infection occurring in patients after admission with other illnesses was not a problem before 1952. Since then numerous cases have occurred. The number of patients admitted with staphylococcal septicæmia has also increased sharply since 1954. Tebbutt could find records of only 18 cases of staphylococcal septicæmia in the years between 1910 and 1928 (Kellaway, MacCallum, and Tebbutt 1928). From 1930 to 1940 there are records of 21 cases—an average of 2 each year. There is no evidence that any of these early cases was infected in hospital.

The present report is based on 86 cases of generalised staphylococcal disease that occurred during the eight years from 1950 to the end of 1957. The patients are divided into two categories: those admitted with infection and those whose infection was acquired in hospital.

TABLE I—ANNUAL INCIDENCE OF GENERALISED STAPHYLOCOCCAL INFECTION 1950–1957

Year	Patients infected outside hospital		Patients infected in hospital		Totals	
	No.	No. of deaths	No.	No. of deaths	No. of patients	No. of deaths
1950	2	2	..	..	2	2
1951	2	..	..	..	2	..
1952	2	2	6	5	8	7
1953	2	1	4	3	6	4
1954	3	1	2	2	5	3
1955	4	1	8	7	12	8
1956	16	9	8	7	24	16
1957	15	3	12	7	27	10
	46	19 (41·3%)	40	31 (77·5%)	86	50

Study of the case-histories, and sometimes the phage-type of the staphylococcus isolated, decided the category of each patient.

The criteria for diagnosis of generalised infection with coagulase-positive staphylococci included one or more of the following:

(1) Clinical evidence of generalised infection together with culture of the organisms from one or more sites.

(2) Growth of organisms from blood-culture.

(3) Pyogenic lesions of the internal organs found at necropsy, together with culture of the organisms from these lesions or from the blood.

All the staphylococci from these patients have been phage-typed and their antibiotic sensitivities determined.

Incidence of Infection

The annual incidence of infection is shown in table I together with the number of deaths; the two categories of patients are shown separately, and the difference in mortality is apparent. The greatly increased incidence since 1955 of patients admitted with infection, and since 1952 of patients infected in hospital, is particularly striking. Our experience differs from that of Wilson and Hamburger (1957) and of Schirger et al. (1957) who report series, from the Cincinnati General Hospital and the Mayo Clinic respectively, in which no increase in annual incidence was observed. The overall mortality in 55 cases at the Cincinnati General Hospital was 71%; in 109 cases at the Mayo Clinic it was 33·9%; in the present series it was 58·1%.

TABLE II—INCIDENCE AND MORTALITY OF STAPHYLOCOCCAL SEPTICÆMIA IN RELATION TO AGE AND SEX OF PATIENTS INFECTED

Age (yr.)	Males				Females			
	Outside infections		Hospital infections		Outside infections		Hospital infections	
	No.	No. of deaths	No.	No. of deaths	No.	No. of deaths	No.	No. of deaths
1–9	2	1	..	..	1	..	..	..
10–19	9	2	4	1	2	..	1	1
20–29	4	2	..	..	4	2	..	..
30–39	4	2	..	..	4	1	5	5
40–49	1	1	6	5	1	1	1	1
50–59	3	3	4	3	2	1	4	4
60–69	3	2	6	4	4	..	1	1
70+	..	..	8	6	2	1	..	..
Totals	26	13	28	19	20	6	12	12

The age and sex distribution of the two groups of patients are shown in table II. There is a fairly uniform age-distribution in cases infected outside hospital, but in hospital-infected cases there is a higher incidence of patients over the age of 30 years. This difference is explained by the age-distribution of patients entering hospital with serious illnesses—particularly those requiring major surgical procedures, which provided the main avenue for cross-infection. The preponderance of males is apparent in each group of patients but is greater in those infected in hospital. All the female patients infected in hospital died.

Patients Infected Outside Hospital

These patients were all seriously ill on admission and usually presented no diagnostic difficulties, particularly when a portal of entry for infection was obvious. The various sites of infection are shown in table III; in 12 patients it was impossible to determine where the septicæmia originated.

The following case is typical of those beginning with a suppurative skin lesion:

A man, aged 37, noticed a few pustules below his left ear on March 1, 1956. Cellulitis followed and soon spread and involved

TABLE III—SOURCE OF INFECTION IN PATIENTS INFECTED OUTSIDE HOSPITAL

Site of initial infection	No. of cases
Boils and carbuncles	10
Other infected cutaneous lesions	9
Respiratory tract	11
Infected miscarriage	1
Puerperal pelvic infection	1
Osteomyelitis (possibly metastatic)	2
Undetermined	12
Total	46

TABLE IV—PHAGE PATTERNS OF STRAINS OF *Staph. aureus* ISOLATED FROM PATIENTS ADMITTED WITH INFECTION

Phage-group	No. of strains	Phage patterns in group
I	3	29, 52/52A/80, 80
II	4	3A, 3B/3C/51, 3C/55, 51
III	13	6/31B/47, 6/47, 6/47/54/75, 7(2)*, 7/31B/47D, 7/42E/47, 7/47/81, 31B, 47, 53, 73, 81
M	1	47A
Not classifiable	24	29/47C, 80/81(22)*, groups I, III, IV
Not typable	1	

* No. of patients.

the back of his neck; despite treatment with penicillin and streptomycin the inflammation extended and he was admitted to hospital on March 9. He was severely ill, confused, and jaundiced, and had a temperature of 103°F; there were pustules below his left ear and there was brawny œdema of the neck and left shoulder. Staphylococci of phage-type 80/81, resistant only to penicillin, were isolated from blood-cultures taken soon after admission, and also from the skin lesions. Treatment with intravenous erythromycin and chloramphenicol resulted in rapid improvement; the fever subsided, the jaundice cleared, and two weeks later the patient was discharged apparently cured. He was, however, readmitted to hospital in July, 1957, with a cerebral abscess due to the same organism.

There were 3 patients in whom staphylococcal septicæmia followed clinical influenza.

A woman, aged 23, developed influenza on Aug. 18, 1957. Two days later she was admitted to hospital with severe pneumonia and died within twenty-four hours despite treatment with intravenous hydrocortisone, chloramphenicol, and erythromycin. A strain of Asian influenza was isolated from tracheal washings taken at necropsy; and staphylococci of phage-type 80/81, resistant to penicillin and the tetracyclines, were grown from the trachea, lungs, and meninges.

Phage-types and Antibiotic Resistance

Table IV shows the phage patterns and the group distributions of the 46 strains of *Staphylococcus aureus* isolated from this group of patients. With two exceptions, none of the many possible phage patterns occurred on more than two occasions. These exceptions were 2 cases infected with phage-type 7, one of which occurred in 1956 and the other in 1957, and, secondly, 22 cases infected with staphylococci of phage-type 80/81. These 80/81 infections comprise almost half the total number of cases. The first 2 cases of 80/81 infection occurred in 1955; and then in 1956 there were 13 people, of whom 7 died, admitted with illness caused by this strain. A high incidence continued in 1957, although in that year there was also an increase in infection with other phage-types.

TABLE V—SOURCE OF INFECTION IN PATIENTS INFECTED IN HOSPITAL

Site of initial infection	No. of cases
Intravenous Infusions:	
Polyethylene tubing (12)	
Metal cannulæ (5)	
Needles (3)	20
Infected surgical wounds:	
Herniorrhaphy	
Nephrectomy	
Lienorenal anastomosis	
Compound fracture of tibia	
Partial gastrectomy	
Drainage of appendiceal abscess	6
Early sequel to Surgical Procedures (72 hours or less):	
Aortic valvotomy	
Mitral valvotomy	
Suprapubic prostatectomy (?)	
Drainage of prostatic abscess	
Left upper lobectomy for pulmonary tuberculosis	6
Respiratory Tract	4
Cutaneous Boil	1
Enterocolitis (following partial gastrectomy)	1
Undetermined	2
Total	40

Only 15 of the strains from these patients were sensitive to penicillin. In 1957 two penicillin-resistant strains were also tetracycline resistant and another was streptomycin-resistant. Resistance to other antibiotics was not found. 3 patients yielded a penicillin-sensitive strain from their first cultures while subsequent cultures of the same phage-type were penicillin-resistant. The phage patterns of these three strains were 7, 7/31B/47D, and 80/81.

Patients Infected in Hospital

All the infections in this group followed surgery, intravenous infusions, or the therapeutic use of cortisone or allied preparations.

The portal of entry of infection is shown in table V; in only 2 cases was the site of infection not apparent.

Of the 20 cases in which septicæmia followed intravenous therapy, polyethylene tubing had been used in 12. This material was chosen only when prolonged infusions were necessary or peripheral veins inaccessible; in all cases saphenous or cephalic veins were used. The fact that longer infusions were possible with polyethylene probably explains the high incidence of infection associated with its use. In the cases so infected, the polyethylene had been inserted in the operating-theatres as often as in the wards.

TABLE VI—PHAGE PATTERNS OF STRAINS OF *Staph. aureus* ISOLATED FROM PATIENTS INFECTED IN HOSPITAL

Phage-group	No. of strains	Phage patterns in group
I	1	52/52A/79/80
III	24	6/7/31B/47, 31B/47(3)*
		47 (with strong phage) (15)*
		47/53/54+ (3)*,
		47/54/70/81, 53
Not classifiable	13	80/81
Not typable	2	

* No. of patients.

There were 9 patients in whom infection followed the use of cortisone for unrelated conditions; these were ulcerative colitis (2 cases), acute leukæmia, chronic lymphatic leukæmia with hæmolysis, severe pneumonia, hypercalcæmia due to malignancy, and postoperative shock where response to other resuscitative measures had been inadequate (3 cases). The patient with pneumonia was the only one to recover.

Slaney and Brooke (1958) reported 8 cases of septicæmia of which 5 were due to *Staph. aureus*. 3 of the patients with staphylococcal septicæmia had been given cortisone in the course of treatment for ulcerative colitis; of these, 1 died.

The following case illustrates the difficulty in diagnosing infection in such patients, where the underlying disease may itself cause fever and the patient is often severely ill from the outset.

A man, aged 52, had had recurrent episodes of diarrhœa with blood and mucus for four years. Six weeks before admission his symptoms became more severe; he was admitted to hospital on Sept. 16, 1956, and on examination was confused and dehydrated and had a temperature of 104°F. Perianal suppuration was present and *Staph. aureus* of phage-type 47/53/54/75 was isolated from this site. A blood-culture taken on admission remained sterile.

An acute exacerbation of chronic ulcerative colitis was diagnosed and treatment commenced with intravenous fluids and oral sulphathiazole. There was only slight improvement, and cortisone therapy was started on the fifth day after admission, together with oral chloramphenicol 2 g. daily. When his condition deteriorated the dosage of cortisone was

TABLE VII—ANTIBIOTIC-RESISTANCE OF STRAINS FOUND IN HOSPITAL-INFECTED PATIENTS

Phage pattern	Antibiotic resistance*	No. of strains
31B/47	R R S S	3
47	R S R S	1
	R R R S	7
	R R R R	7
47/53/54+	R R R S	2
	R R R R	1
80/81	R S S S	2
	R R S S	2
	R R R S	4
	R R R R	1
	R R S R	1
	R S S R	1

*Resistance (R) or sensitivity (S) to penicillin, streptomycin, the tetracyclines and chloramphenicol in that order.

increased, but no further blood-cultures were taken. On Sept. 28 the patient developed boils on his back, from which a penicillin-resistant and streptomycin-resistant staphylococcus of phage-type 80/81 was isolated.

The patient died on Oct. 8, and at necropsy was found to have severe ulcerative colitis with perforation of the large bowel. There were also subcutaneous abscesses and pyæmic lesions of the lungs and prostate, from which staphylococci of phage-type 80/81, resistant to penicillin, streptomycin, and chloramphenicol, were isolated.

Phage-types and Antibiotic Resistance

In contrast to the diversity of strains found in patients admitted with infection, the staphylococci isolated from cross-infected patients belonged to only a few types (table VI). In 1950, before these serious infections commenced, the chief cross-infecting staphylococci in this hospital were penicillin-resistant and streptomycin-resistant and of phage pattern 31B/47, 31B, or 47; late in 1951 strains resistant also to the tetracyclines and sometimes to chloramphenicol and typing only with undiluted phage 47 made their appearance (Rountree et al. 1951, Rountree and Thomson 1952). These strains were responsible for most of the serious cross-infections until 1955 when the type 80/81 strains, which had been introduced into the hospital in the preceding year (Rountree and Freeman 1955), caused 5 cases. Since then phage 80/81 strains and strains belonging to phage-group III and typing as 47 or 47/53/54+ have accounted for the majority of cases. In the remainder, four strains were of other patterns and two were not typable; 5 of these patients were transferred from other hospitals where they had been infected, but they have been counted in the group of those infected in hospital. The cross-infecting strains characteristic of this hospital were all penicillin-resistant and displayed a wide range of resistance to other commonly used antibiotics (table VII).

Clinical Features

In general, the clinical picture of infection in the patients studied was similar to that described in other series of cases of staphylococcal septicæmia (Wilson and Hamburger 1957, Schirger et al. 1957); no important differences were observed between the two categories of patients in the present series except for the site of initial infection (tables III and V).

TABLE VIII—CUTANEOUS MANIFESTATIONS OF STAPHYLOCOCCAL SEPTICÆMIA

Type of lesion	No. of cases
Pustules	2
Petechiæ and purpura	5
Osler's nodes	2
Urticaria	4
Ecchymoses	1
Subcutaneous abscesses	3
Diffuse erythema	7

Rigors were a prominent symptom in half the total number of patients, and fever was a feature in all except 5. Seldom below 101°F, the temperature was of the swinging or spiked variety in a third of patients, irregular in the remainder. Of the 5 patients who remained afebrile throughout their hospital stay, 4 died; absence of fever was not due to cortisone, as none of the afebrile patients had received steroids before septicæmia developed.

Splenomegaly was noted in only 5 patients, excluding 3 in whom the spleen was enlarged because of underlying diseases.

Pericardial friction was heard in 3 patients and pericarditis found at necropsy in 5 others.

Various cutaneous manifestations occurred (table VIII); these were mostly non-specific and seldom helpful in diagnosis.

The present study emphasised the fact that staphylococcal septicæmia presents few characteristic features; early diagnosis depends on considering the possibility of this disease in any patient with fever which is not otherwise readily explained.

Bacterial endocarditis was diagnosed in 3 patients who recovered and in 1 who died without necropsy being performed. Endocarditis was found at necropsy in 9 cases, in 4 of which the condition had been unrecognised during life. The process was described as subacute in 2 cases, and acute in the remainder. Evidence of pre-existing valvular disease was present in only 2 of the patients who died with endocarditis.

This study did not support the experience of Wilson and Hamburger (1957) that cerebral involvement in staphylococcal septicæmia was rare unless endocarditis also was present. In the present series there was evidence of meningeal or cerebral abnormality in 13 patients, of whom only 3 had endocarditis.

Treatment

Correct therapy depends on establishing the antibiotic sensitivity of the infecting organism. Since treatment in these cases is urgent and must be started before this information is available, it is important to use drugs which are most likely to be effective. The choice must therefore be based on past experience of the sensitivities of the commonest strains.

Penicillin is not now used initially. If, however, the organism proves to be penicillin-sensitive, this antibiotic is given in large doses—up to 50 million units intramuscularly per day and, rarely, 100 million units daily by intravenous infusion; it must be remembered that such large doses of penicillin intravenously may cause convulsions. Since 1955, in only 10 of the 35 cases infected before admission was the staphylococcus penicillin-sensitive; in only 1 patient of the whole series infected in hospital was the staphylococcus penicillin-sensitive.

Since the infecting organism may be resistant also to the tetracyclines, and since the majority of these patients are extremely ill, initial treatment is now recommended with both chloramphenicol and erythromycin, preferably parenterally. Dosages of up to 4 g. daily of each have been used, and with clinical improvement these may be replaced by normal dosage by mouth. Other of the newer antibiotics, such as novobiocin, may be indicated subsequently, according to the result of the sensitivity tests and the patient's response to treatment.

Antibiotics are continued for two weeks after clinical recovery and for not less than three to four weeks in all.

In patients with endocarditis treatment for at least six weeks is considered necessary.

Staphylococcal antitoxin was used in a few cases, but without apparent benefit. It seems reasonable to recommend its use in cases with apparently overwhelming infections accompanied by toxæmia.

In conjunction with appropriate antibiotics, cortisone is indicated in shocked patients, in those desperately ill at the time of admission, and, in particular, in those with staphylococcal pneumonia following influenza. Cortisone may be used also in cases which have responded poorly to antibiotic therapy, where a fatal outcome appears likely, though less imminent, than in the circumstances mentioned above. The following case directed attention to the value of steroid therapy in this situation (a similar result was obtained in another patient):

A man, aged 53, underwent a lienorenal anastomosis for portal hypertension on April 4, 1957. Postoperatively his wound became infected with staphylococci of phage-type 80/81, sensitive to the tetracyclines, chloramphenicol, and erythromycin. Rigors then developed, and his temperature rose to 104°F; there was clinical and radiological evidence of widespread pneumonia. From cultures of sputum and blood staphylococci were isolated, of the same phage-type and antibiotic sensitivity as the organisms grown from the surgical wound.

There was no clinical response to full doses of chloramphenicol, erythromycin, and novobiocin; the patient's condition deteriorated, and treatment with prednisone was started a week after infection became manifest. Chloramphenicol and erythromycin were continued at the same time.

The fever subsided promptly, and his clinical condition improved remarkably; but attempts to withdraw prednisone resulted in recurrence of fever, although further blood-cultures remained sterile. Treatment with prednisone, chloramphenicol, and erythromycin was continued for two months in all, then gradually withdrawn. The patient was discharged three months after operation and has remained well.

Discussion

The present series of cases confirmed an impression that staphylococcal septicæmia had increased in recent years. Previous studies of the epidemiology of staphylococcal infection in Australia provide a basis for assessing the relative importance of the factors contributing to this increased incidence. In 1953 and 1954, infections with a new strain of *Staphylococcus aureus* occurred in maternity hospitals (Isbister, Durie, Rountree, and Freeman 1954, Rountree and Freeman 1955) and the strain responsible was identified with a new phage, 80. Most strains of this type are also lysed by phage 81 (Bynoe et al. 1956) and can therefore be described as phage-type 80/81. These strains are now widespread, not only in Australia (Rountree and Beard 1958) but also in other countries (Blair and Carr 1958).

The whole of the increased incidence of staphylococcal septicæmia in patients admitted with infection in 1955 and 1956 was due to strains of this type. In 1957 seven other types were also found, but two of these were closely related to the 80/81 strain. In contrast to the cases of septicæmia admitted before 1955, in which the portal of entry of the organism could rarely be determined, infections with phage-type 80/81 strains commonly started as simple infections of the cutaneous tissues and were followed rapidly by septicæmia.

In addition to the cases reported here, there was also a number in which this strain caused fatal staphylococcal pneumonia (Purser 1958). Gresham and Gleeson-White (1957) have described cases of staphylococcal pneumonia in which death occurred without previous clinical evidence of acute infection. Some of the cases at this hospital presented a similar picture; these have not been included in the present series as there was no bacteriological evidence of involvement of tissues other than the respiratory tract, but they emphasise the pathogenicity of this particular staphylococcus. Nevertheless the prognosis among patients admitted with infection was not significantly worse in those infected with 80/81 strains (43·5% of whom died) than it was in those infected with various other phage-types (39% of whom died).

It can be concluded that the chief factor responsible for the increase in staphylococcal septicæmia in patients infected outside hospital was the appearance of this new strain and its spread in the general community. On the other hand, the increased incidence of generalised infection in hospital-infected patients is due to the interaction of several factors. These include: (1) the establishment in the hospital environment of strains of staphylococci with multiple antibiotic resistance, and consequent failure of antibiotic " covers " for surgery; and (2) the increased use of protracted intravenous therapy. Improvements in surgical techniques have made possible long operations on patients who previously would have been considered inoperable, and whose clinical condition may have lowered their power to resist staphylococcal infection. In several cases in this series there was little doubt that the administration of cortisone had contributed to the loss of defensive mechanisms normally inhibiting invasion by staphylococci.

The prognosis for patients infected in hospital was clearly poorer than for those admitted with infection, the mortality-rate in the former being 77·5% compared with 41·3% in the latter. Nevertheless, in 1957 there was an improvement in the death-rate of those infected in hospital: 5 out of 12 patients recovered, compared with only 4 of the 28 infected in previous years. This improvement coincided with increased awareness of the problem of cross-infection at this hospital, leading to earlier diagnosis of septicæmia and aggressive treatment with appropriate antibiotics.

In only 1 patient cross-infected in hospital was there evidence of staphylococcal enterocolitis, which has been reported in other countries as a cause of fatal hospital infection (Cook et al. 1957). Where organisms from such cases have been phage-typed they have been shown to belong to phage-group III, but they have been of different patterns from the group-III strains found here. This suggests that not all strains of group-III staphylococci may be capable of causing staphylococcal diarrhœa.

The many cases of staphylococcal septicæmia diagnosed in 1952–57 underline the magnitude of the staphylococcal problem and the potential seriousness of infection with these bacteria. Possibly our experience may not be representative of that in other hospitals and localities. This is a large teaching hospital, and some of the patients in the present series were transferred from other hospitals where they had become infected; and a few of those infected outside hospital had been transferred from the country. These cases were, however, only a small proportion of the whole series, and there seems no doubt that the increase in incidence of these infections in New South Wales is real.

Summary

In the eight years from 1950 to 1957, 86 cases of staphylococcal septicæmia were diagnosed in one hospital.

40 patients were infected in hospital and 31 (77·5%) of

them died. The infecting staphylococci belonged to only a few phage-types. These infections started in 1952 and all followed surgery, intravenous therapy, or the exhibition of cortisone.

46 patients acquired their infections outside hospital and 19 (41·3%) died. Up to 1954 there was an average of 2 such cases each year, but the incidence rose notably in the three following years. This increased incidence was due almost entirely to infections with strains of phage-type 80/81.

In 1957 mortality-rate in both categories of patients fell. This decline coincided with keener awareness of the problem of staphylococcal cross-infection, earlier diagnosis of septicæmia, and intensive treatment with effective antibiotic combinations.

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SEX REVERSAL IN NEWBORN BABIES

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SEX reversal may be detected in the newborn by the sex-chromatin test (Moore et al. 1953, Moore and Barr 1955). The validity of this test of chromosomal sex has been confirmed by several other investigators (Emery and McMillan 1954, Sohval et al. 1955, Lennox 1956, Segal and Nelson 1957, Silagy and Chiang 1958, and others). Sex reversal is seldom detected in the newborn because it is rarely associated with other recognisable congenital abnormalities. It is usually detected in adolescents with abnormalities of sex development. Sex reversal may be suspected in some girls at birth, or during childhood, if they show clinical characteristics of gonadal dysgenesis (Turner's syndrome and related conditions). A sex-chromatin test would reveal whether sex reversal had occurred.

Sex reversal was suspected in man before a method of detecting it was introduced (Jost 1950, Wilkins 1950). They suggested that some patients with gonadal dysgenesis, although anatomically female, might be chromosomal males. This possibility was suggested after Jost had shown that male rabbit fœtuses always developed into females when they were castrated at a sufficiently early stage of development.

Polani et al. (1954) were the first to test the chromosomal sex of patients with gonadal dysgenesis; they found that all 3 of their patients were chromosomal males. However, it was soon shown that not all patients with this disorder are chromosomal males; for in several investigations, taken together, about 20% of them were chromosomal females (Grumbach et al. 1955, Barr 1956). The chromosomal males are thought to begin as male embryos, and then develop into essentially normal-appearing girls when testes fail to differentiate.

Apparent females with so-called "testicular feminisation" (Morris 1953) may also be thought of as instances of male-to-female sex reversal (*Lancet* 1958). These patients are often classified as male pseudohermaphrodites, but they differ from the latter in some important respects. They appear normal at birth, and develop into essentially normal-appearing women (Morris 1953, Nelson 1956). Their male chromosomal sex and gonads are usually detected only when they present themselves with inguinal herniæ or amenorrhœa. These patients are thought to originate as male embryos, and then to feminise when the fœtal testes fail to secrete the hormones or inductor substances essential for the differentiation of male accessory sex organs.

Sex reversal in apparent males is now very well known. The observation that some patients with Klinefelter's syndrome had chromatin-positive nuclei, the female type (Plunkett and Barr 1956, Bradbury et al. 1956), stimulated considerable interest in this disorder (*Lancet* 1956). Originally this condition was thought to be quite rare, but many cases were soon reported (Riis et al. 1956, Jackson et al. 1956, Nelson 1956, Grumbach et al. 1956, Ferguson-Smith et al. 1957, Raboch 1957, Beattie 1957). These reports showed that not all patients with this syndrome were chromatin-positive, and that conversely many patients were chromatin-positive who did not fit the Klinefelter syndrome. Numerous names have been used to describe these patients, because of the variation in characteristics from patient to patient. Testicular dysgenesis is the name used in the remainder of this paper; this term is preferred because it denotes imperfect development of testes, a characteristic feature of all such cases.

The histological structure of the testes has varied from one patient to another, but the main defect has been fibrosis and hyalinisation of the seminiferous tubules. Germ-cells have been absent or scarce in most cases, but complete spermatogenesis has been observed in isolated portions of some patients' tubules. Spermatozoa have never been observed in semen samples from these patients. Men with chromatin-positive nuclei and testicular dysgenesis apparently begin development as female embryos; then testes mysteriously develop which secrete the necessary hormones or inductor substances causing development of male accessory sex organs.

Attempts have been made to estimate the frequency of chromatin-positive males in the general population. Ferguson-Smith et al. (1957) suggested that at least 1 in every 10,000 males is chromatin-positive, whereas Prader et al. (1958) thought the incidence may be as high as 1 in 1000. The incidence appears to be higher among mentally defective persons than in the general population. The results of two surveys of these patients were: 4 in 325 males (Ferguson-Smith 1958), and 8 in 336 males (Prader et al. 1958).

In the present investigation chromosomal sex of infants was tested in order to detect sex reversal in the newborn. The purpose was to determine whether there is any hitherto undescribed association between sex reversal and

any evident congenital abnormality, and to determine the incidence of sex reversal in these newborns.

Methods

Oral smears were collected over a period of twelve months from the 3715 babies (1911 males and 1804 females) born at the Winnipeg General Hospital.

The smears were prepared by scraping the oral mucosa with a sterile nickel spatula, and smearing the material over a relatively small area of a clean microscope slide. Each smear was fixed immediately in equal parts of ether and 95% ethyl alcohol, the fixation extending overnight. The smears were stained with cresyl echt violet, using the staining procedure described in an earlier paper (Moore and Barr 1955).

Each smear was examined under the oil-immersion objective of a binocular microscope for the presence or absence of visible sex chromatin. The anatomical sex of the infant was unknown to the microscopist at the time of the examination. Sex-chromatin counts were not made routinely, because the chromosomal sex was usually obvious. However, at least 100 nuclei were examined from each infant before a diagnosis of sex was made. Additional smears had to be collected in some cases because the routine ones were not of sufficiently high technical quality. When the chromosomal-sex diagnosis differed from the anatomical sex of an infant, several more smears were collected. Some of these smears were stained by the Feulgen method for confirmatory observations.

The chromosomal sex was recorded on the infants' charts in all sex-reversed cases. Infants with a chromosomal sex opposite to their anatomical sex were given a special examination by the medical staff of the department of pediatrics. The parents of the sex-reversed infants were not informed of the discrepancy, and confirmatory biopsies were not done, because unnecessary attention, especially after the babies had left the hospital, might have caused some concern to the parents. Gonadal biopsies were impracticable in all cases, because clinically these babies were normal.

Observations

Apparent males.—In 5 of 1911 males tested, typical female-sex chromatin was observed; the chromosomal sex was male in all the other anatomical males. Amongst the 5 chromatin-positive males, the proportion of nuclei counted exhibiting female-sex chromatin varied from 53% to 64%. Moore and Barr (1955) have found that even in people that were females both chromosomally and anatomically the proportion of nuclei showing female-sex chromatin varied from 40% to 60%.

All the pregnancies producing the 5 chromatin-positive males were uncomplicated. All were single-birth full-term infants. The only abnormal finding was the presence of female-sex chromatin in their nuclei. The external genitalia were entirely male in appearance, and normal in size for newborns. The testes had descended into the scrotum in all infants, and were normal in size and consistence on palpation.

Apparent females.—The female-sex chromatin was a conspicuous feature of many nuclei of all 1804 females, and had the characteristics described by Moore and Barr (1955).

Discussion

Incidence

The incidence of chromatin-positive males in 1911 newborn males was 0·26%. The frequency of sex reversal in anatomical males born at this hospital was calculated from table v of Mainland et al. (1956) to be between 0·06% and 0·74%. These percentages represent the lower and upper 1% confidence limits. In a further publication the incidence of sex reversal in the present series of newborn males will be compared with the incidence in male mental defectives, in whom higher frequencies have been reported. Some of the chromatin-positive males in the present series may later show mental retardation; this will be discussed in the paper under preparation.

The results of the present investigation seem to indicate that female-to-male sex reversal is commoner than male-to-female sex reversal, for no sex-reversed males were detected in the 1804 anatomical females tested. The upper confidence limit of sex reversal in apparent females born at this hospital was calculated from table IX of Mainland et al. (1956) to be 0·29%. A larger number of observations would improve this estimate, especially if broader sampling of the general population were achieved.

Probable Future Development of Chromatin-positive Newborn Males

Most of the chromatin-positive males reported before this series have been postpubertal, and have shown clinical characteristics of testicular dysgenesis. Only a few prepubertal cases have been reported, and they have been essentially normal-appearing boys; but, after chromatin-positive oral smears, histological evidence of testicular dysgenesis has been found in 2 cases (Bunge and Bradbury 1957, Ferguson-Smith 1958). It is generally held that all chromatin-positive males have or will develop testicular dysgenesis; but this may not be so. Some chromatin-positive males may develop normally, and be indistinguishable from normal males except by their female-sex chromatin. If all 5 chromatin-positive males in the present series develop testicular dysgenesis, then the incidence of this condition must be higher than is generally thought at present.

There is some evidence to support the possibility of fertility in chromatin-positive males. Spermatogenesis has been observed in testicular biopsies from a few patients; in most of them it has been incomplete, but spermatozoa have been seen in some (Bunge and Bradbury 1956, Nelson 1956, Ferguson-Smith et al. 1957, Segal and Nelson 1957). All these patients have been sterile, but so are all patients with testicular dysgenesis whether they are sex-reversed or not. The finding of spermatogenesis in chromatin-positive males shows that fertility is possible in such males, if the testes were to develop normally. It is known that some sex-reversed fishes and amphibians have the ability to reproduce (Witschi 1939, Chang and Witschi 1956).

The offspring of a chromatin-positive male should all be chromosomal females, for such males could produce only X-type spermatozoa. These statements are true only if the sex chromatin in his cells represents 2 X-chromosomes. The origin of sex chromatin is not definitely known, but it is generally thought to be a reliable indicator of female chromosomal sex (Moore and Barr 1954, Lennox 1956, Sachs and Danon 1956, Segal and Nelson 1957). Although a fertile chromatin-positive male should produce all females, the possibility that he may produce chromatin-positive males like himself cannot be excluded.

These considerations suggest that the 5 chromatin-positive males in the present series will probably show normal sex development until puberty. Some will probably develop characteristics of testicular dysgenesis during adolescence, but others may become normal-appearing fertile males.

Ætiology of Female-to-male Sex Reversal

The ætiology is not known, but several hypotheses have been suggested. Most of the suggestions have been concerned with chromosomal abnormalities, probably

because differentiation of the gonads is generally thought to be genetically controlled. Stewart et al. (1958) have admirably discussed the various chromosomal hypotheses, and have proposed a new one based on their genetical studies. Stewart et al. also adduce some evidence of familial transmission of testicular dysgenesis in chromatin-positive males.

Early deficiency of primordial germ-cells in the gonads has been suggested as a causative factor for sex reversal in patients with testicular dysgenesis (Witschi 1956, Witschi et al. 1957). These investigators have also suggested various factors which might cause a reduction in the number of primordial germ-cells in the gonads of man.

The following is a further contribution to speculation concerning the ætiology of female-to-male sex reversal in man. It is well known that hormones from hyperplastic fœtal adrenals cause masculinisation of the external genitalia of females; similar effects have been observed in girls whose mothers have been treated with steroids during pregnancy (Wilkins et al. 1958, Gold and Michael 1958, Nellhaus 1958). The gonads were not affected in any of the above cases, apparently because the hormones acted after the direction of differentiation of the gonads was determined. In some masculinised females the source of the hormones was not detected; Wilkins et al. (1958) have suggested that in these cases there may be an abnormal metabolism of maternal or placental hormones during pregnancy, resulting in the formation of androgenic substances. If this were to arise early enough, these androgens might cause the indifferent gonads of female embryos to develop as testes, eventuating in complete masculinisation of all accessory sex organs. It is well known that partial gonadal sex reversal in the freemartin of cattle (a chromosomal female) is caused by fœtal testicular secretions from a male twin (Lillie 1917, Moore et al. 1957). Furthermore, androgens administered to genetic female frogs at a critical stage in development caused testes to differentiate instead of ovaries (Witschi 1951). Thus hormonal imbalance may possibly cause female-to-male sex reversal in man.

Probable Prenatal Development of Chromatin-positive Males

The chromosomal sex of these infants, established at fertilisation, was female. During early gonadal differentiation some factor caused the cortices of the indifferent gonads to degenerate; then testes differentiated from the medullary regions. The testes secreted hormones or inductor substances which caused complete differentiation of male accessory sex organs. The testes descended into the scrotum at the normal time, and the chromosomal females had the anatomical appearance of normal males.

Summary

The chromosomal sex of 3715 newborn infants (1911 males and 1804 females) was detected by the oral-smear technique of Moore and Barr (1955).

All except 5 of the infants had a chromosomal sex consistent with their anatomical sex. The 5 exceptions were all anatomical males; they were normal-appearing infants but had sex chromatin patterns typical of chromosomal females. They are regarded as instances of female-to-male sex reversal.

It is suggested that some of these chromatin-positive males are likely to develop characteristics of testicular dysgenesis during adolescence; some may also become mentally subnormal. The possibility of such males developing normally is also discussed.

Most writers suggest that female-to-male sex reversal is caused by chromosomal aberration; other possibilities are discussed, and a hypothesis of hormonal imbalance is offered.

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THE PREPUBERTAL TESTICULAR LESION IN CHROMATIN-POSITIVE KLINEFELTER'S SYNDROME (PRIMARY MICRO-ORCHIDISM) AS SEEN IN MENTALLY HANDICAPPED CHILDREN

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THE finding of chromatin-positive Klinefelter's syndrome (primary micro-orchidism) in just over 1% of male patients in a mental-deficiency hospital (Ferguson-Smith 1958) has led me to try to ascertain the frequency of the condition among the much larger number of mental defectives who remain out of hospital. At the same time, opportunity has been taken to learn more about the nature and time of onset of the testicular lesion. I hoped that, as it is now possible to diagnose the condition before puberty by nuclear sexing techniques, means might be found to prevent or modify the invariable

SPECIAL INVESTIGATIONS

Case	Age at biopsy (yrs. mos.)	Mental age (yrs. mos.)	I.Q.*	Testis size† (mm.)		Urinary F.S.H. (mouse units per 24 hours)	Urinary 17-keto-steroids (mg. per 24 hours)
				Right	Left		
1	7 0	4 8	65	13	15	<10	1–2
2	8 6	5 6	66	14	13	<10	2
3	8 10	6 6	74	14	14	..	2–3
4	9 8	5 0	51	14	14	<10	2
5	10 8	6 3	58	18	18	<10	2
6	11 4	8 9	77	..	14	<10	3–4
7	11 8	7 0	62	17	17	<10	2
8	12 0	6 6	50	25	24	10–20	6

F.S.H. = follicle-stimulating hormone.
* Intelligence quotient assessed by Terman Merrill revision of the Stanford-Binet scale.
† Length measured at exposure during biopsy.

sterility (at least in those with normal intelligence) and the often distressing stigmata of gynæcomastia, eunuchoidism, and androgen deficiency observed in adult patients.

The relatively high incidence among mental defectives has been confirmed in a similar survey by Prader et al. (1958) who found 8 cases among 336 feebleminded boys (2·4%), and independently by Cornwell and Herrmann (1958) who describe 3 cases detected clinically in a training school for the mentally retarded. The frequency of the condition among persons with normal intelligence is harder to assess. It is clearly high enough to be important, however, for investigation of a male infertility clinic showed that approximately 3% of all subfertile patients had female nuclear sex (Ferguson-Smith et al. 1957). Certainly no more than a quarter of these patients showed signs of subnormal intelligence and some appeared to have more than average intelligence.

There has been much speculation about the nature, or even the existence, of a testicular lesion before puberty (see particularly de la Balze et al. 1952, Grumbach et al. 1957, Witschi et al. 1957). As the micro-orchidism and other clinical features are not usually apparent until adolescence, the only means of detecting prepubertal cases is by demonstrating female nuclear sex. In the general population opportunities for this are few, and in fact only 1 early case had been reported (Bunge and Bradbury 1957) before systematic survey of mental defectives uncovered another (Ferguson-Smith 1958). Testicular biopsies in 2 more cases (aged 11 and 13) have now been described by the Zurich group; they interpret the histological appearances as indicating that the testes in chromatin-positive cases (with female nuclear sex) are normal until puberty, when development of the characteristic tubular hyalinisation is preceded by regression of the germinal epithelium (Siebenmann and Prader 1958). Close study of the evidence presented by these workers, and examination of testicular biopsies in 8 cases found in the present survey, suggests that this conclusion is unjustified. In the cases so far investigated a testicular abnormality could be demonstrated long before puberty.

Incidence

The nuclear sex was determined, by the oral-mucosal-smear technique (Moore and Barr 1955), in 85% of all male children between the ages of 5 and 12 attending special schools for the mentally handicapped in Glasgow. The intelligence quotient of these children ranged from 45 to 85. Of the 663 children examined, 8 were found to have female nuclear sex, giving an incidence of 1 in 83 or 1·2%. In this age-group there were at this time, according to the records of the school medical department, 63,070 male children in Glasgow, and thus the frequency in this sample of the general population must be at least 1 in 6640. Other cases no doubt exist among defective children showing a greater degree of mental defect, who, being ineducable, do not attend the special schools and so are not included in the survey. In addition, judging by the proportion of adult cases with normal intelligence, there must be at the very least an equal number in this population attending schools for normal children. On the basis of an earlier investigation (Lennox et al. 1958) we concluded that the incidence in Glasgow could not be less than 1 in 10,000. Our present figures raise our estimate of *minimum* incidence to 1 in 3000. It may well be considerably higher.

Clinical Features

7 of the 8 chromatin-positive cases showed no obvious related physical abnormality. Case 6 was overweight and only one testis could be found in the scrotum; the right testis was impalpable and presumably undescended, although the possibility of true hermaphroditism with unilateral testis cannot be excluded without further investigation. All cases, including the oldest (case 8), are prepubertal and show no evidence of development of secondary sex characteristics.

I have not been able to obtain measurements in a complete range of normal testes, but the testicular lengths in these chromatin-positive cases, as measured at exposure for testicular biopsy (see table I), seem to be much smaller than controls of comparable age at present available. Unfortunately this difference in size is not sufficiently obvious clinically to be as helpful in diagnosis as it is in

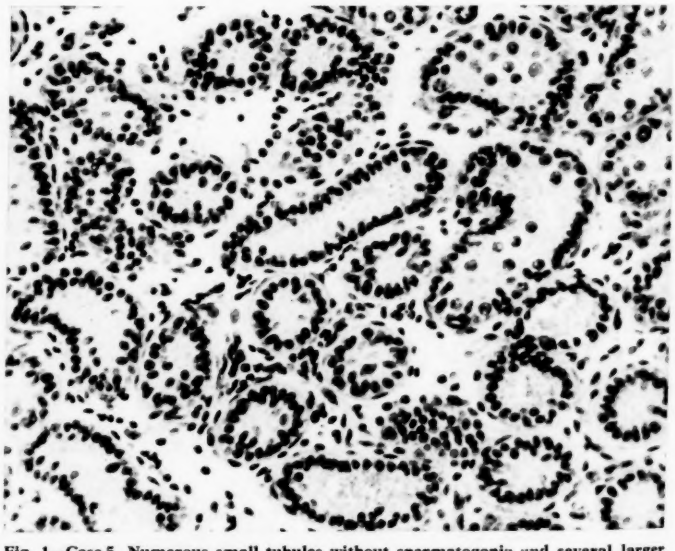

Fig. 1—Case 5. Numerous small tubules without spermatogonia and several larger "fertile" tubules (upper right) with a normal complement of spermatogonai. Hæmatoxylin and eosin. × 245.

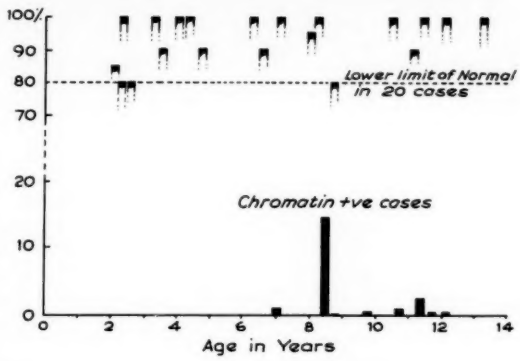

Fig. 2—Percentage of "fertile" tubules in normal controls and in cases 1-8.

postpubertal chromatin-positive cases. It provides some justification, however, for continuing to group these cases under the term chromatin-positive micro-orchidism in preference to Klinefelter's syndrome, which, as originally described (Klinefelter et al. 1942), does not exist as a clinical syndrome before puberty, and exists in only a proportion of chromatin-positive cases after puberty. Further details, including hormone assays, are recorded in table I.

Testicular Histology

Testicular biopsies were obtained in all cases, and the histological appearances were compared with those of testes from 20 necropsies on male children dying from conditions in which there was no particular involvement of the gonads. None of the chromatin-positive cases show normal testicular histology. The most obvious and significant abnormality is a reduction in germinal cells, amounting to absence in case 3. In 6 cases, two clearly defined types of seminiferous tubule can be identified (fig. 1); the majority are smaller than normal controls of the corresponding age, contain no spermatogonia, and are lined exclusively by undifferentiated Sertoli cells; standing out among these "sterile" tubules is a very occasional "fertile" tubule which is about the same size as the normal control and contains a normal complement of spermatogonia, the spherical nuclei and usually clear cytoplasm of the latter contrasting with the closely packed oval nuclei of the supporting Sertoli cells. It is possible to estimate the proportion of seminiferous tubules which show spermatogonia on cross-section. All the controls assessed in this way contain at least 80% of "fertile" tubules and most contain over 90% (fig. 2). The highest proportion of "fertile" tubules in the chromatin-positive group is found in case 2, but this does not exceed 20%. All tubules are "sterile" in the biopsy material from case 3, and in the remaining 6 cases "fertile" tubules do not exceed 5%.

The testicular appearances in the oldest patient (case 8), aged 12 at the time of biopsy, are of additional interest and show a more advanced lesion. At this age, and before the appearance of secondary sex characteristics, the normal testis usually shows evidence of maturation with enlargement of tubules, differentiation of the Sertoli and Leydig cells, and active division of germinal cells. These maturation changes are present also in case 8, except that there is a virtually complete absence of germinal cells; in some areas there is commencing tubular hyalinisation and several newly formed small "ghost" tubules without elastic tissue are seen. These histological changes are associated in this case with abnormally high urinary gonadotrophins. I hope to present later a more detailed study of the changes which lead to the characteristic testicular appearance in the adult: they are clearly of some complexity.

In 5 of the 8 cases, biopsy specimens contain structures resembling corpora amylacea. These appear to be within the seminiferous tubules and probably represent products of the tubular epithelium retained in the more severely dysgenetic tubules. They stain strongly by the periodic-acid-Schiff method, and the apparent "nuclei" are consistently Feulgen-negative. Similar structures are occasionally seen in normal prepubertal testes and in cryptorchids, and without more positive evidence the suggestion that these are "ova" (Bunge and Bradbury 1957) does not seem to be acceptable.

Discussion

The main purpose here is to demonstrate that a defect already exists in the prepubertal testis of chromatin-positive cases. Although it is unwise to prophesy sterility in a patient known to have germ-cells, however few, the reduction in the normal complement of spermatogonia in these children is probably sufficient for a forecast of gross infertility, if not sterility, and treatment is unlikely to influence this. As they grow older and approach puberty, the judicious use of androgens may be of benefit in producing normal development of secondary sex characteristics and preventing disproportionate growth in adolescence.

No relation is found between the age of the child and the proportion of tubules containing spermatogonia; and, although the youngest case observed was 7 years old, it is probable that in each the complement of germ-cells does not vary significantly from birth or even earlier. At first this deficiency of germ-cells seems to support the suggestion of Witschi et al. (1957), from experiments on amphibia, that sex differentiation (depending on the relative supremacy of the cortex or medulla of the developing fœtal gonad and the resultant induction of the genital ducts and external genitalia along male or female lines) depends on the number of primordial germ-cells; this in turn is said to be adversely affected by degradation of the ovum either initially or at an early stage of embryogenesis. Against this point of view is the observation that such a deficiency in germ-cells before puberty is not confined to chromatin-positive cases, but is common to several other types of testicular dysgenesis; for I have seen almost exactly the same histological features in cases of true cryptorchidism and in 3 prepubertal cases of testicular feminisation (Morris 1953). It is also very probable that cases of true lateral hermaphroditism and of chromatin-negative micro-orchidism (Ferguson-Smith et al. 1958) show the same defect at this stage. In view of the wide variation in sex differentiation, ranging from the most extreme cases of male pseudohermaphroditism (e.g., testicular feminisation) to near-normal men complaining of infertility, these almost identical prepubertal testicular findings seem to indicate that the number of primordial germ-cells is not the fundamental controlling factor in sex differentiation. These also indicate that although a deficiency in germinal cells is an important associated defect, it cannot be considered the cause of chromatin-positive micro-orchidism and the apparent sex reversal: the primary disorder in

this condition has still to be discovered. They indicate, again, that, in some if not all cases of true cryptorchidism (as opposed to ectopic testes and retractile testes), deficiency of germ-cells is an inherent defect rather than the result of a progressive degenerative process due to the abnormal position of the testis as is generally supposed (see, for example, Brunet, de Mowbray, and Bishop, 1958).

The changes which occur at puberty in chromatin-positive micro-orchidism are complex, and their proper consideration must await additional cases. In the patients so far investigated tubular hyalinisation has by this time usually become quite conspicuous. In this respect there is a clear difference from the chromatin-negative group in which tubular hyalinisation occurs less often, and much later, as is readily shown by studies on the tubular elastic tissue (Ferguson-Smith et al. 1958).

Summary

The frequency of chromatin-positive micro-orchidism (Klinefelter's syndrome) among 663 male prepubertal children attending special schools for the mentally handicapped was determined by the oral-mucosal-smear technique of nuclear sexing and found to be 1·2%.

In the 8 cases discovered, testicular biopsy was performed. Comparing the histological appearances with those of 20 normal testes obtained at necropsy, the most significant difference was a big reduction in the complement of spermatogonia. Such a deficiency of germinal cells is seen in other varieties of testicular dysgenesis before puberty, and so cannot be considered the primary cause of chromatin-positive micro-orchidism.

In children with chromatin-positive micro-orchidism maturation of the testis, at about the age of 12, appears to be followed by tubular hyalinisation.

The significance of these findings is discussed in relation to treatment, to the ætiology of cryptorchidism, and to sex differentiation.

This survey would have been impossible without the most willing cooperation of Dr. James Ewan, principal medical officer, Glasgow School Health Service, Mr. James A. Stewart, his assistant administrative officer, and the head teachers and staffs of the special schools visited. I am also most grateful to Mr. W. S. Mack for testicular biopsies, to Dr. A. D. T. Govan for hormone assays, Mr. Andrew McGhie for intelligence testing, and Dr. A. M. MacDonald and Dr. James A. Imrie for necropsy material.

Finally I wish to record my sincere thanks for the personal interest and encouragement of Dr. Bernard Lennox, whose work on nuclear sexing initiated the study of which this is a part.

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EFFECT OF NICOTINIC ACID ON SERUM-LIPIDS IN NORMAL AND ATHEROSCLEROTIC SUBJECTS

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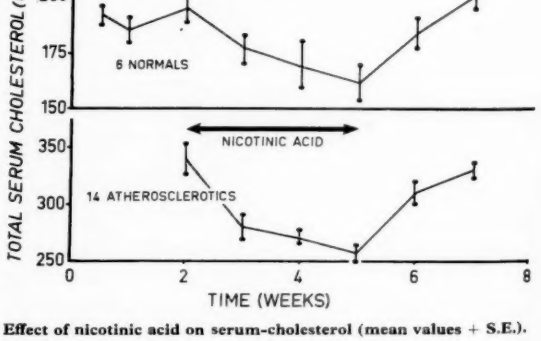
IN 1955 Altschul et al. reported that large doses of nicotinic acid, administered to normal subjects, led to prompt reduction in the level of serum-cholesterol. This has been confirmed and extended to include hypercholesterolæmic subjects (Parsons et al. 1956, O'Reilly et al. 1957, Comesana et al. 1958). As nicotinic-acid therapy is simple and inexpensive and any potential treatment of atherosclerosis is worth investigating, it was decided to examine further the effect of large doses of nicotinic acid on the serum-cholesterol levels of both normal subjects and a group of atherosclerotic individuals, and to study the effect of nicotinic acid on the total serum-lipids and the β-lipoproteins.

Material and Methods

The subjects of the investigation were two groups consisting of eight male medical students with an average age of 22 and fourteen atherosclerotics (nine males and five females) aged 36–71. All the atherosclerotics had serum-cholesterol levels above 250 mg. per 100 ml.

All subjects in both groups had blood samples taken before, during, and after exhibition of nicotinic acid (see accompanying figure). Nicotinic acid was given in doses of 1 g. three times daily. While taking nicotinic acid each subject continued on his usual diet, and in none of the subjects was there any change in body-weight during the time of the study.

The blood was analysed for total serum-cholesterol by the method of Pearson et al. (1953). Total serum-lipids were measured by the turbidimetric method of Kunkel (1937), and lipoproteins were determined in duplicate by paper electrophoresis in a barbitone buffer at pH 8·6. The separated lipoproteins were stained with oil red O dye, and the stained lipoprotein strips were analysed with an automatic scanning device, the ' Spinco Analytrol '.



Effect of nicotinic acid on serum-cholesterol (mean values + S.E.).

Results

The accompanying figure shows the effect on serum-cholesterol levels. In the eight normal subjects following initiation of nicotinic-acid therapy there was a fall in the serum-cholesterol which was statistically significant (P 0·05). Discontinuance of nicotinic acid was followed by a return to pre-treatment values. In the fourteen atherosclerotic subjects the cholesterol level fell significantly (P 0·01) during treatment with nicotinic acid, and returned to previous values when this ceased. Administration of nicotinic-acid was also associated with a reduction in the total serum-lipids, the level of which returned to normal after administration was stopped.

In the eight normal subjects the β-lipoprotein lipid, expressed as a percentage of the total lipoprotein lipid, decreased from 73% to 65% (P 0·05) during administration of nicotinic acid, with a return towards pre-treatment values after the drug was stopped. In the fourteen atherosclerotic subjects administration of nicotinic acid was followed by a decline in the percentage of β-lipoprotein lipid from 80% to 72% (P 0·02) at the second week of treatment. When the nicotinic acid was stopped the β-lipoprotein lipid rose to pre-treatment levels.

Discussion

Almost all subjects had side-effects—vasodilatation and pruritus. These effects were less pronounced when the nicotinic acid was taken simultaneously with food, and practically disappeared at the end of the first week of the therapy. The atherosclerotic group complained little about these side-effects, but the control group of medical students were most vocal in their complaints.

These results agree with those of Altschul et al. (1955) and Parsons et al. (1956). Achor et al. (1958) have shown a reduction in β-lipoprotein cholesterol and total lipids as well as serum-cholesterol following nicotinic acid. Some of their patients had been on nicotinic acid for as long as nine months and maintained low levels of serum-cholesterol during this time. After the nicotinic acid was discontinued there was a prompt return to pre-treatment level.

The mechanism of action of nicotinic acid in reducing serum-lipids is unknown. Altschul (1958) suggests that nicotinic acid increases the concentration of coenzymes I and II of which it is an integral part, and this results in greater oxidation of cholesterol to more readily excretable steroids. Merrill and Lemley-Stone (1957) have postulated that nicotinic acid depletes the body of methyl and acetyl groups. This hypothesis is based on a finding that nicotinic acid is excreted partially as a methyl derivative. The observation that nicotinamide is ineffective in lowering serum-lipids (Comsena et al. 1958), whereas nicotinic acid is effective, is difficult to reconcile with both these hypotheses. The efficacy of nicotinic acid in lowering serum-cholesterol has now been well confirmed. It is also apparent, however, that in many hypercholesterolæmic atherosclerotic subjects so treated the serum-cholesterol still remains increased above the normal range. Whether maintaining a lowered serum-cholesterol by means of nicotinic acid improves the prognosis of atherosclerosis remains to be established.

Summary

Nicotinic acid in doses of 3 g. daily for two to three weeks caused a prompt reduction in total serum-cholesterol, total serum-lipids, and β-lipoprotein lipid in eight normals and fourteen atherosclerotic subjects.

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CHOLESTEROL-BINDING CAPACITY OF NORMAL AND ATHEROSCLEROTIC INTIMAS

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Two groups of causes may be responsible for the development of atherosclerosis—changes in the blood and changes in the blood-vessel wall. Those who lay the blame mainly on the blood point to the deranged fat and cholesterol metabolism in patients with atherosclerosis: abnormalities in the quality and quantity of circulating blood-lipids are reflected in the raised blood-cholesterol (Boas et al. 1948, Hueper 1949, Hirsch and Weinhouse 1943), the abnormal electrophoretic pattern of the plasma-proteins (Barr et al. 1951), and the increase in the lipoprotein fraction on ultracentrifugation (Gofman 1950, Gofman et al. 1950). The plasma-phospholipids, moreover, are diminished (Gertler et al. 1950, Gertler and Lerman 1950); and the colloidal equilibrium of the lipoproteins may be so disturbed as to favour their precipitation.

Among the changes in the blood-vessel wall, alterations in its ground-substance have received much attention in recent years. The mucopolysaccharides of the intima are increased and polymerised (Schwarz and Dettmer 1953), and this might explain a raised lipid-binding capacity (Bürger 1939, Faber 1949). The atherosclerotic vessel may contain up to seven times the normal quantity of lipids (Windaus 1910); and these can be shown to be bound to globulins.

The purpose of my investigation was to determine whether this increased lipid content is due to a change in the globulins of the atherosclerotic ground-substance or, more simply, to an increased entry of lipids from the blood into the vessel-wall.

Material and Method

Normal and atherosclerotic human aortas were studied.

Collection of Material

Immediately after death the aorta was removed from the body and washed in water. The intima was carefully dissected off the media, cleared from blood with saline, and dried with filterpaper. Extracts were then prepared, using known quantities of dried intima and physiological saline, for electrophoresis and chemical analysis.

Electrophoresis of Intimal Extracts

Using the Shandon apparatus, a current of 150 V was allowed to pass for twenty hours: a 'Whatman 31' filterpaper and 'Veronal' buffer (pH 8·6) were used. The strips were stained with bromphenol-blue for proteins and sudan-black for lipids.

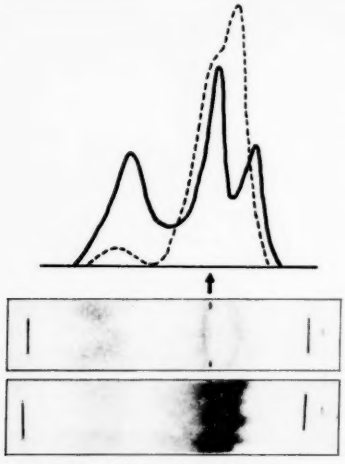

Fig. 1—The electrophoretic pattern of an extract made from normal intima. The continuous line in the graph is the proteinogram and the dotted line the lipidogram.

Chemical Analysis of Extracts

The cholesterol, total-lipid, and globulin content of each extract was estimated; and the amount of lipid and globulin corresponding to 1 g. of intima, and the amount of cholesterol and lipid corresponding to 1 g. of globulin, were calculated.

The intimal extracts were washed with ether, and the ether extracts were separated from the proteins and evaporated to dryness. The lipid fractions thus obtained were then redissolved in the aqueous phase containing the proteins of the intima. The unchanged electrophoretic mobility of these proteins showed that washing with ether had not significantly denatured them.

After the lipid fraction had been redissolved in the aqueous phase, the electrophoretic pattern of the proteins was unchanged and showed that the lipids were again bound to the globulin fraction. By estimating the cholesterol, total-lipid, and globulin content of this solution the cholesterol-binding and lipid-binding capacity of the intimal globulins could thus be determined.

Results

On electrophoresis the proteins extracted from normal intimas separated into three fractions: all three contained lipids (fig. 1). The electrophoretic pattern of extracts from atherosclerotic intimas usually showed only one: this differed from any of the normal fractions by showing no electrophoretic mobility whatever at pH 8·6. A second, very small fraction appeared in some cases, but this contained no lipids (fig. 2).

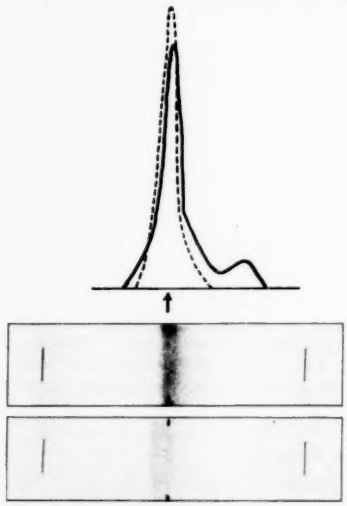

Fig. 2—The electrophoretic pattern of an extract made from atherosclerotic intima. Continuous line: proteinogram. Dotted line: lipidogram.

Tables I–III show the composition and lipid-binding capacity of normal and atherosclerotic intimas. It will be seen that the mean cholesterol, total-lipid, and globulin content of 1 g. of normal intima was 1·4 mg., 3·5 mg., and 32 mg., and that the corresponding figures for atherosclerotic intimas were 7·1 mg., 27·8 mg., and 32 mg., The mean values of cholesterol and total lipids combined with 1 g. globulins from normal intimas were 44 mg. and 109 mg. respectively. The corresponding figures for globulins from atherosclerotic intimas were 356 mg. and 1147 mg.

TABLE I—COMPOSITION OF NORMAL AND ATHEROSCLEROTIC INTIMAS

Type of intima	—	Quantities in 1 g. of intima		
		Cholesterol (mg.)	Total lipids (mg.)	Globulins (mg.)
Normal (from 5 aortas)	Range	0·73–2·00	2·25–4·50	27–36
	Mean	1·40	3·50	32
Atherosclerotic (from 6 aortas)	Range	3·20–12·80	21·00–32·60	29·80–36·00
	Mean	7·10	27·80	32

TABLE II—LIPIDS BOUND TO 1 G. OF GLOBULIN IN NORMAL AND ATHEROSCLEROTIC INTIMAS

Type of intima	—	Cholesterol (mg.)	Total lipids (mg.)
Normal (from 5 aortas)	Range	27–60	84–134
	Mean	44	109
Atherosclerotic (from 6 aortas)	Range	107–432	700–990
	Mean	225	876

Conclusions

There is a sharp difference in the electrophoretic pattern of globulins extracted from normal and from atherosclerotic intimas, and this can be accepted as evidence of differences in structure. Weight for weight, atherosclerotic intimas contain five to seven times more lipids than normal ones. Electrophoresis suggests that the lipids are bound to globulins; and I was able to show that globulins from atherosclerotic intimas can bind more lipids than globulins from normal intimas, even when the latter are allowed to combine with lipids from atherosclerotic material.

TABLE III—LIPIDS BOUND TO GLOBULIN IN ETHER EXTRACTS OF DIFFERENT INTIMAS REDISSOLVED IN THE PROTEIN-CONTAINING AQUEOUS PHASES OF DIFFERENT INTIMA EXTRACTS

Source of lipids and of globulins *	Cholesterol (mg.)		Total lipids (mg.)	
	Range	Mean	Range	Mean
Lipids from normal intimas: globulins from atherosclerotic intimas	185–368	258	925–1068	994
Lipids from atherosclerotic intimas: globulins from atherosclerotic intimas	225–460	356	1082–1195	1147
Lipids from atherosclerotic intimas: globulins from normal intimas	75–128	103	152–278	222

* Five experiments were performed for each of the three combinations.

These findings support the view that changes in the globulins of atherosclerotic intimas—especially their raised lipid-binding capacity—may account for the deposition of lipids in atherosclerosis.

I am grateful to Prof. Sedat Tavat, head of department, for his interest and encouragement in this work.

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PANIC AND PHOBIA
A POSSIBLE METHOD OF TREATMENT

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IN a subject as little mapped as psychiatry, ideas of more general importance can sometimes evolve from consideration of quite limited clinical problems. In this paper I shall discuss a method for the management of students with acute examination panic. This condition, though never common, is well known to physicians in university practice, and is generally recognised as most difficult to treat. The student is not just strained and anxious; he is obsessively terrified by the impending examination, often to the point of complete incapacity. The standard methods of sedation, reassurance, and support that seem to work so well with ordinary cases of subacute pre-examination strain (Malleson 1957) leave these poor people untouched. Despite our best efforts they are often unable to get to the examination room or, if they get there, are unable to sit through the examination.

I have used another approach in a number of cases, any of which would do for presentation here. But because it was the first, and the most florid, the case of an Asian technology student has been chosen.

He had an Indian degree, but was here to take an English qualification. He had been some 5 or 6 months in the country and had failed his main professional examination soon after arrival because of an acute attack of panic similar to that about which he consulted me. Apart from this he had been in excellent health and good spirits during his time in England.

When he was brought to my consulting-room by a fellow student he was classically panic-stricken, showing nothing to suggest physical disease. I prescribed sedatives, reassured him strongly and sent him home. Later that evening his friend telephoned to say he was " feverish " and " very bad " apparently just as he had been before his previous examination. " Would I go to his lodgings at once ?" Sure enough, he was feverish; his temperature was 102 F. He was shivery, and his teeth were chattering. But his symptoms otherwise were not those of a high fever; they were those of high panic. He was sobbing and tearful, bewailing his fate, terrified of the impending examination, desperate that the " fever " would stop his getting there, and asking about the possibility of ægrotat degrees. Careful clinical examination failed to reveal anything suggestive of organic disease, and nothing to suggest malaria save his black skin. His condition was regarded as simply that of mounting panic. (Some people do not recognise psychogenic fever in adults; I am sure they are mistaken.)

With only 48 hours to go before the examination, and this his last chance of sitting, and in view of his rapid deterioration despite sedation, it seemed that something more dramatic should be risked, and a new approach was therefore tried.

In the first world war " shellshock " cases, it will be remembered, were at first taken right away from the military atmosphere. They were sent to comfortable convalescent homes in Scotland, and sheltered from newspapers and war talk. They were given sedatives, and everything was done to make them feel relaxed and calm. But they did extremely badly. Later, the technique of making them face, recall, and, if need be, abreact the occasions of their fears enormously improved the prognosis. Working on the same principle, I felt that perhaps we should not comfort, protect, and cosset these students, but encourage them to experience their fear as fully as possible. From ideas first suggested to me by the clinical psychologist Peter Fletcher, I had come to suspect that the complex of feeling what we call " fear " or " panic " is always integrally bound up with the wish to escape. So long as that wish persists, reciprocally the fear persists. Perhaps therefore if a patient could be persuaded to accept a fearful situation, and allow himself to experience fear without trying to avoid it, the vicious circle of fear leading to the escape urge leading to more fear could be unwound. (The footsteps that follow one in a country lane after dark become louder and more menacing the more one hurries. Only when one stops and permits them to approach do they fade from the imagination.)

Something of this principle was explained to the student. He was made to sit up in bed, and to try to feel his fear. He was asked to tell of the awful consequences that he felt would follow his failure—derision from his colleagues in India, disappointment from his family—financial loss. Then he was to try to imagine these things happening; try to imagine the fingers of scorn pointed at him, his wife and mother in tears. At first, as he followed the instructions, his sobbings increased. But soon his trembling ceased. As the effort needed to maintain a vivid imagining increased, the emotion he could summon began to ebb. Within half an hour he was calm. Before leaving I instructed him in repeating the exercise of experiencing his fears. Every time he felt a little wave of spontaneous alarm he was not to push it aside, but was to enhance it, to augment it, to try to experience it more profoundly and more vividly. If he did not spontaneously feel fear, every 20 or 30 minutes he was to make a special effort to try and do so, however difficult and ludicrous it might seem. I arranged to see him twice a day over the next 2 days until his examination.

He was an intelligent man, and an assiduous patient. He practised the exercises methodically, and by the time of the examination he reported himself as almost totally unable to feel frightened. He had, as it were, exhausted the affect in the whole situation. He passed his examination without apparent difficulty.

The Mechanism of Phobias

In dealing with acute pre-examination cases, one cannot avoid the impression that the patient's fear has the curious illogical quality that constitutes a phobia, but with the addition of a panic state. People who suffer from simple monophobias usually manage to avoid contact with the object of their phobia—their spiders or black cats—or at any rate they are able to beat a very rapid retreat. But the student with an examination phobia is trapped in his fearful situation. He is in panic because the inexorable ticking of the clock is bringing him ever nearer to the dreaded inescapable engagement with his examiners. With this superimposed panic reaction excluded, the picture of persistent irrational fear (which the subject himself may well recognise to be groundless but is nevertheless unable to combat by conscious effort) is very similar to the common phobias syndrome. This similarity has led me, in a limited way, to try a similar therapeutic approach.

In my practice the only suitable cases have been sufferers from agarophobia or claustrophobia. Although such situational phobias are usually part of a wider distress and do not lend themselves as readily as would the object phobias, the results so far have been most encouraging. (Fletcher tells me he first used the method with an apparently complete cure in an intelligent young woman with a cat phobia that had for years seriously limited her daily life.)

Phobic states are notoriously difficult to treat, as psychotherapists of all schools have testified. Whether the original precipitating fear arose from an objective event (an attack by a savage tomcat on the patient when young in Fletcher's case), or, as is more common, from an inward subjective fear explicable in terms of unconscious symbolism, therapy usually brings little amelioration to the phobic symptom pattern itself even where good insight seems to have been gained. One is tempted to believe that, superimposed upon the initiating psychodynamics, there is some circular mechanism which, once set up, is self-perpetuating.

There are many classical experiments with laboratory animals which could be regarded as the simplest analogue of some such circular mechanism. For example, a rat, trained by shocks from an electrified floor grid, will repeatedly jump out of the experimental box; and the reaction can then persist indefinitely without any repetition of the original noxious stimulus. One presumes that in the box the rat " expects " to be hurt, and feels its own ratty sort of fear. Jumping out sends away this fear, thus reinforcing the escape response by the ordinary mechanism of drive reduction. Similarly, in man, the sending away of fear could provide the self-winding mechanism that keeps a phobia going. The sufferer from a cat phobia, for example, on getting near to a cat, or to a place where he suspects a cat will be, feels mounting fear. With it comes the urge to escape. As he turns and hurries away, his immediate fear feeling is dispersed. If it is as I have argued with the examination cases, the seeking of escape validates the fear. Potentially strengthened and enhanced, this fear remains inside ready to be re-experienced at his next encounter. By such a cycle (fear/escape-urge/more fear) phobic patterns could become established.

The Therapeutic Technique

Working on such a thesis, and proceeding along the lines described for the examination panic cases, the patient is helped to break the phobic cycle by having him make a deliberate effort to feel and to experience fully his fear without trying to escape from it. In practice, I have started by getting to know the patient and his difficulties in the ordinary psychotherapeutic manner during the first few interviews. As far as possible personal and psychodynamic problems, which always exist, are relieved. The exact dimensions and circumstances of his recurring phobia pattern are next carefully defined. The principles are explained simply and clearly, much as written above, to ensure full intelligent participation. He is then instructed to expose himself progressively to his phobic situation or object. As he does so, he has to attend most actively and fully experience the unpleasant emotions and all the concomitant bodily sensations that are aroused in him. An agarophobic patient, say one who cannot walk from home to his place of work alone, is told to go to the foot of his front-door steps. When he has felt all the fear possible there—and cannot feel more, so bored of it he has become—he is to advance twenty-five yards or so down the pavement, or until the fear is rekindled. There again he is to stand still and experience his emotions, and so on. In my patients, so far, a very small amount of assiduous practice has reduced the phobic difficulty to manageable proportions, and has sometimes freed ordinary life from much restriction.

It is important to make clear to patients that the aim of the exercises is to experience the fears and all the bodily sensations that always accompany them, and not simply to achieve such-and-such a distance, or such-and-such a contact. One often meets people, particularly those with phobias of situation rather than object (for situations are less easily avoided than objects) who say they *can* do so-and-so if they have to; but the mere doing of it does not at all reduce the phobic abhorrence for the next time. This, I think, is because they force down the feeling of fear by sheer willpower, doggedly attending instead to the material goal. Although such a person may not be escaping the fearful situation, he is, in some measure, escaping the fear of it by an act of dissociation; but this leaves the circular mechanism unbroken. For therapy, however, full attention to and experience of the internal unpleasantness is essential.

My experience has been that this approach, being a method of symptom treatment, is only likely to succeed with the patient whose phobia is well demarcated and is, of itself, a substantial disability. A large number of neurotic patients show phobic-reaction patterns, often transient, to a variety of situations which are bound up with their interpersonal problems. Such patients do not seem to benefit; at the best they merely exchange one phobia for another.

The Mechanism of Therapy

The subtle pattern of inward fear that originally kicks off a phobia may be best explained in psychodynamic terms. But the circular mechanism I have hypothesised is best stated in the terms of learning theory. The therapeutic method, although devised on empirical clinical grounds in the first instance, is also open to a rudimentary explanation in Hullian terms.

Fear, as it is felt, and with all its body concomitants, is a learned response. Like all responses, it engenders reactive inhibition (I_R). In the phobic situation the characteristic rapid and early escape so quickly disperses the fear that very little reactive inhibition has time to build up. There is therefore no adequate opportunity to develop a habitual mechanism for inhibiting the fear ($_sI_R$). In the therapeutic exercises, the deliberate experiencing of the fear for as long and as intensively as possible permits the generation of reactive inhibition, subjectively experienced as boredom. The moment of time in which the fear fades away to be replaced by another thought or feeling becomes rewarding. There is in treatment a period when the subject is trying to feel the fear but his " mind keeps wandering ". As this happens, I presume the habit of fear inhibition ($_sI_R$) is being generated. Thereafter the response of fear and the concomitant wish to escape that the phobic object produces becomes progessively tempered by an opposite learned response—one of familiarity, lack of interest, and boredom—in short " not fear ".

One could well suppose that by such a mechanism all situations which are initially new and frightening become ordinary and acceptable with experience. The phobic state, as a pathological mechanism, comes about only when the escape response acts so briskly that the fear can never rise enough to be tempered by experiential learning.

If an explanation of this kind was true, one would expect those people whose nervous systems are naturally given to excitatory processes, and in whom inhibitory mechanisms are less evident, to be the ones who most easily develop phobias. Eysenck, in his General Theory (1957), postulates that the introversion/extraversion continuum is a reflection of the excitatory/inhibitory variation in different people. He evinces arguments to show that hysterics have high extraversion scores and high inhibitory levels, whereas dysthymics and obsessionals have high introversion scores and low inhibitory levels. Although I know of no specific data published on the extraversion/

introversion ratings of phobic patients, the phobias as a clinical group are classified by all authorities with the obsessional neuroses. If Eysenck's view that obsessionals are low in inhibition is accepted, support is lent to the hypothesis.

If treatment works in the manner I have suggested, it could, for want of a better name, be called " reactive inhibition therapy ". That would place it, as a parallel, alongside some of the methods described by Wolpe (1958) under the title of " reciprocal inhibition therapy ". But I would not wish it to be regarded as a principle of psychotherapy complete in itself. It is merely a psychiatric instrument, available for selective use, like hypnosis, sedation, or reassurance.

Conclusions

A hypothesis of this kind, tenuous as it is, has two points to commend it. First, it is clinically fertile; it suggests a technique for treating a group of conditions otherwise hard to relieve. Second, it can be tested by clinical trial. Unlike many other psychiatric conditions, improvement by treatment (in the monophobic states at least) can be measured on relatively simple objective criteria. Also, the essential technique of fear-experience—the reactive inhibition therapy—is something separate from and additional to the more general non-specific effects of the psychotherapeutic contact. It should therefore be possible to compare an experimental and a control group both having the common background of the doctor-patient relationship. Ideally I should have presented such a trial series in this paper; but there are too few cases in a university practice. Only someone working in a psychiatric unit proper is likely to have access to a sufficient number.

Summary

A new approach to the treatment of acute examination panic in students is described. Because of the similarity between this condition and phobic states in general, a similar therapeutic approach for phobias is suggested. A possible mechanism for the development of phobic symptom patterns is outlined, and an explanation for the effect of therapy, couched in terms of Hullian learning theory, is put forward. The term " reactive inhibition therapy " has been coined to describe the principle followed, and suggestions made for more adequate clinical trial.

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". . . Cooperation among governments, though subject to interruption by major differences, does not depend upon political harmony, on an identity of interest, or on similarity of social systems. It rests upon identifiable, reciprocal, practical advantages. Cooperation belongs as much to the hard-headed realist as to the warm-hearted idealist. A nation's own postal system is severely limited unless its mail can move readily to foreign destinations. Nations which oppose each other with great bitterness nevertheless join in an epidemiological reporting service. If politics can disrupt cooperation, it is equally true that habits of cooperation in everyday affairs lay a moderating and restraining hand upon political crisis. If present danger, therefore, lends urgency to the great issues of war and peace, prudence suggests that as much as possible be done to broaden and deepen the base of cooperation. Man at his best may thus find something worthwhile to say to man at his worst."—DEAN RUSK in the president's review from the Rockefeller Foundation Annual Report, 1957; p. 4.

USE OF VENOUS BLOOD FOR pH AND CARBON-DIOXIDE STUDIES

ESPECIALLY IN RESPIRATORY FAILURE AND DURING ANÆSTHESIA

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THE assessment of respiratory function and acid-base equilibrium may depend on measurements of the arterial-blood oxygen tension (pO_2), oxygen saturation, carbon-dioxide tension (pCO_2), and pH. Combined with other tests on blood (e.g., the electrolytes) these can depict the metabolic aspects of respiratory function under all clinical conditions, and may also clarify the underlying pathophysiology in a way not possible by symptoms, clinical examination, or X-rays. There is no doubt of their value in the treatment of patients; nevertheless, pH and respiratory blood-gas studies are almost entirely confined to research units and special centres. Undoubtedly the technical difficulties of the estimations have been a bar to their wider use, but improvements in methods have largely solved this problem, at least in the case of pH and pCO_2 measurements. These two estimations alone can be extremely helpful clinically. The purpose of this paper is to show that in certain circumstances the estimations may be performed on venous blood and that arterial blood is not essential.

It is generally agreed by pulmonary physiologists that the arterial pCO_2 measures alveolar ventilation more conveniently than does the arterial pO_2. pCO_2 is easier to measure than pO_2; it is less subject to limitations imposed by pulmonary arteriovenous shunts, variations in the distribution of blood and gas within the lungs, and barriers to diffusion across the alveolar-capillary membrane. A most important advantage is that the pCO_2 can be used as an index of alveolar ventilation in patients breathing oxygen-enriched mixtures.

At rest the arterial pCO_2 at sea level deviates little from 40 mm. Hg. A value appreciably greater than this denotes alveolar hypoventilation, and a value below 40 mm. Hg denotes alveolar hyperventilation. Both alveolar hypoventilation and hyperventilation are common disorders, and it may be impossible to detect them without laboratory aids.

Arterial pCO_2 may be estimated directly (for example, by bubble-equilibration techniques); but the estimate is more easily derived indirectly from two measurements—of the plasma pH and of the plasma total CO_2 (TCO_2) content. The plasma pH can be measured directly on blood in a few minutes using methods designed for continuous operation (Astrup 1956, Wynn and Ludbrook 1957). The estimation of TCO_2 is routine in most clinical laboratories and presents no special difficulty. The pCO_2 can now be calculated by means of the well-known Henderson-Hasselbalch equation relating pH, TCO_2, and pCO_2, or a graphic representation of this relationship (a nomogram can be used). Therefore the estimation of pCO_2 adds only one further technique to routine clinical biochemistry—namely, the pH determination.

We thought it would simplify the problem if venous rather than arterial blood could be used for pH and pCO_2

determinations. Venepuncture is generally easier than arterial puncture, especially in inexperienced hands, and repeated arterial puncture in the same subject is undesirable. We took as our starting-point the old observation that " arterialisation " of peripheral venous blood can be achieved by suitably heating the hand and arm (Meakins and Davies 1919-20, Dautrebande et al. 1923, Goldschmidt and Light 1925). The method described by earlier workers, however (soaking the hand and arm in hot water), is cumbersome, and the temperature recommended (46°C) was higher than many of our patients could tolerate. We therefore tried lower temperatures and used electric pads which could be used without constant supervision. We also investigated the possibility of spontaneous " arterialisation " of venous blood, and found that this occurred, a striking example being during general anæsthesia.

Methods

The hand and forearm were heated by two electric 'Thermega' pads loosely bound round the limb but separated from the skin by the sleeve of pyjama or bedjacket. The heating lasted 15 minutes. The temperature beneath the pads did not exceed 40°C. The temperature of the skin of the dorsum of the hand was measured (to the nearest 0·5°C) by gently pinching the skin into a furrow into which a mercury thermometer was inserted. After the heating period the skin temperature reached about 38°C. Venous blood was taken from a vein on the back of the hand or wrist of the heated limb, and sometimes from a similar site on the unheated limb as well. Venous stasis was avoided. Arterial blood was obtained by brachial or femoral artery puncture. Blood from each site was taken anaerobically into a heparinised syringe well lubricated with silicone grease. The pH was measured by the method of Wynn and Ludbrook (1957). The syringe containing the blood was spun in the centrifuge and the separated plasma transferred anaerobically into a Van Slyke pipette for the estimation manometrically of its total CO_2 content by the method of Van Slyke and Neill (1924). The analyses were performed in duplicate. The pCO_2 was calculated from the rearranged Henderson-Hasselbalch equation:

$$pCO_2 \text{ mm. Hg} = \frac{TCO_2 \text{ mM/l.}}{[1+\text{antilog } (pH-6{\cdot}1)]\ 0{\cdot}0301}$$

Results

Arteriovenous (A.V.) Differences in Plasma pH, TCO_2, and pCO_2 in Ambulant Subjects Before and After "Arterialisation" of Venous Blood

The five subjects whose results are shown in table I, group A, were ambulant patients with minor illnesses. They had, prior to the test, been sitting or standing about the ward, and for this study lay on their beds while the hand and arm were being heated. The arteriovenous differences after heating are small, and probably the agreement is close enough for most clinical purposes. The figures in parentheses are the results on venous blood obtained from the unheated hand. The arteriovenous differences are much larger than in the former comparison, showing that the heating had an effect in promoting " arterialisation " of venous blood.

A.V. Differences Before and After " Arterialisation " of Venous Blood in Patients Confined to Bed

The subjects whose results are given in table I, group B, were convalescent (four patients) or were moderately to severely ill (five patients). The main difference between them and the previous group studied was that they were confined to bed for the test. In these nine patients the A.V. differences after heating were even less than in the former group of patients and in all cases the differences were insignificant. The A.V. differences, however, in the case of the unheated hand (the results in parentheses in table I) were quite large. The patients in groups A and B showed that it was feasible to " arterialise " venous blood so that A.V. differences in pH and pCO_2 became negligible after a short period of heating. In this respect there

TABLE I—ARTERIOVENOUS DIFFERENCES IN PLASMA pH, TCO_2, AND pCO_2 IN FIVE GROUPS OF PATIENTS

Group	No of cases	Skin temperature (°C)		Arteriovenous differences					
				pH		TCO_2 (mM/l.)		pCO_2 (mm.Hg)	
		Mean	Range	Mean •	Range	Mean •	Range	Mean •	Range
A	5	38·2	38·0–38·5	0·018 (*0·061*)	+0·012 (+*0·038*) to (*to*) +0·024 (+*0·083*)	1·3 (*2·4*)	−0·7 (−*1·9*) to (*to*) −2·1 (−*3·1*)	3·5 (*9·6*)	−3·0 (−*6·3*) to (*to*) −4·8 (−*11·4*)
B	9	38·4	38·0–38·5	0·002 (*0,045*)	±0·000 (+*0·021*) to (*to*) +0·008 (+*0·062*)	0·4 (*1·2*)	±0·0 (−*0·3*) to (*to*) −0·7 (−*2·2*)	0·8 (*6·7*)	±0·0 (−*5·5*) to (*to*) −2·1 (−*9·1*)
C	7	35·2	35·0–35·5	0·010 (*0·001*)	±0·000 (±*0·000*) to (*to*) +0·037 (+*0·002*)	0·2 (*0·00*)	−0·4 to +0·5	1·2 (*0·1*)	+0·9 (±*0·0*) to (*to*) −2·4 (−*0·2*)
D	1	34·2 (*35·5*)	34·0–34·5	0·063 (*0·003*)	+0·024 to +0·073	3·7 (*0·3*)	−2·2 to −5·0	16·9 (*0·1*)	−10·8 to −21·2
E	10	35·4	35·0–35·5	0·002	±0·000 to +0·009	0·3	−1·1 to +1·0	1·1	−1·1 to +5·0

TCO_2 = Plasma total CO_2 content.

pCO_2 = Plasma carbon-dioxide tension.

• Sign was disregarded in calculating the mean.

Group A.—The patients were convalescent and were ambulant prior to the test. " Arterialisation " of venous blood was achieved by a period of heating (see methods). The skin temperature was taken at the back of the hand at the time of venesection and is highest in groups A and B because of the local heating. Figures in parentheses refer to measurements on venous blood obtained simultaneously from the contralateral (unheated) hand.

Group B.—Four of the patients were convalescent and five were moderately to severely ill. All were confined to bed prior to the test. " Arterialisation " of venous blood was achieved by heating, and the figures in parentheses refer to measurements on venous blood obtained simultaneously from the contralateral (unheated) hand.

Group C.—These patients were all severely ill and were confined to bed but had warm extremities. Venous blood was obtained from the back of an unheated hand. The skin temperature was taken at the back of the hand at the time of venesection. Figures in parentheses refer to blood taken from the contralateral (heated) hand.

Group D.—This patient had advanced emphysema and cor pulmonale. Observations were made on the patient on four separate occasions while he was ambulant and on a fifth occasion (results are given in parentheses) when the patient had been confined to bed for one hour.

Group E.—These patients were operated upon under general anæsthesia (see text).

TABLE II—ARTERIOVENOUS DIFFERENCES IN PLASMA pH, TCO_2, AND pCO_2 IN PATIENT X WITH SEVERE EMPHYSEMA, BRONCHITIS, AND COR PULMONALE

Date (December, 1957)	pH		A.V. pH	TCO_2 (mM/1)		A.V. TCO_2 (mM/1)	pCO_2 (mm. Hg.)		A.V. pCO_2 (mm. Hg.)
	A.	V.		A.	V.		A.	V.	
7	7·374	7·370	+0·004	42·3	42·4	−0·1	71·1	71·8	−0·7
8	7·380	7·363	+0·017	40·5	40·1	+0·4	67·1	68·9	−1·8
18	7·275	7·267	+0·008	40·5	41·5	−1·0	84·4	87·8	−3·4
20	7·302	7·305	−0·003	40·4	40·5	−0·1	79·5	79·1	+0·4
24	7·304	7·306	−0·002	47·9	48·9	−1·0	93·8	95·3	−1·5
31	7·350	7·336	+0·014	49·7	49·9	−0·2	88·1	91·0	−2·9

The venous blood was obtained from the back of an unheated hand.

seemed to be an advantage if the patient was confined to bed before the test.

A.V. Differences in Patients with Spontaneous "Arterialisation" of Venous Blood

The seven patients in group C, table I, were severely ill and confined to bed. In all the patients, however, the extremities and general body surface were warm, the superficial veins were full, and the skin temperature over the dorsum of the hand was 35°C (or a little more). Without prior heating the A.V. pH and pCO_2 differences in these patients were negligible, and heating of the limb produced an insignificant effect (the results are given in parentheses). These cases showed that the heating procedure was unnecessary providing that the patient was confined to bed, and the cutaneous circulation was sufficient to produce a warm skin generally and a temperature over the dorsum of the hand of at least 35°C.

Influence of High Arterial pCO_2 on A.V. pH, TCO_2, and pCO_2 Differences

Hypercapnia is known to cause peripheral vasodilatation and anoxæmia (which is always found in patients breathing air who are underventilating), and is usually associated with an increased cardiac output. It seemed reasonable to suppose therefore that in hypoventilation spontaneous "arterialisation" of peripheral venous blood might occur. This is not the case inevitably, however, as is shown by the results given in table I, group D. The patient suffered from advanced emphysema and cor pulmonale. At rest his arterial pCO_2 was about 66 mm. Hg and his oxygen saturation 80–85%. He was ambulant prior to the first four tests performed on him. His skin temperature when measured was below 35°C and the A.V. pH and pCO_2 differences were very large. When the patient was confined to bed for 90 minutes before the final test (the results are given in parentheses in table I) the A.V. differences disappeared. In this test the patient's skin temperature was a little higher than in the previous studies; but another important factor may have been the prolonged rest, since this patient's oxygen saturation fell greatly with only moderate exertion. We conclude, therefore, that a high pCO_2 and high cardiac output are not in themselves followed by spontaneous "arterialisation" of peripheral venous blood and that rest in bed and a high skin temperature (at least 35°C) is necessary.

It is well known that general anæsthesia usually results in vasodilatation and a high cutaneous blood-flow. We decided to see whether this observation could be utilised to obtain "arterialised" venous blood without any special heating of the limb. Ten cases were studied consecutively, blood being taken from a vein at the back of the hand and from the femoral artery at various times during general anæsthesia. Anæsthesia was induced in all cases with thiopentone and maintained with nitrous oxide, oxygen, and a relaxant. Some of the patients received pethidine and others halothane or trichloroethylene in addition. The duration of anæsthesia before venepuncture varied from 20 to 180 minutes. The A.V. differences in pH, TCO_2 and pCO_2 were insignificant, despite the extreme levels encountered in some of the patients. The range of pH found was from 6·786 to 7·437 and of pCO_2 from 137 mm. Hg to 34·1 mm. Hg. The anæsthetised patients had a high skin temperature, and we conclude that during general anæsthesia spontaneous "arterialisation" of venous blood occurs, at any rate so long as other factors do not reduce the skin blood-flow, which would be indicated by a fall of skin temperature below 35°C.

Having established some of the facts about arteriovenous blood pH and pCO_2 differences, we set out to see how the information could be applied to patients.

Case X (table II) was a seriously ill man with chronic bronchitis, emphysema, and cor pulmonale. He was extremely dyspnœic, anoxæmic, and either semicomatose or comatose for about five weeks but finally improved considerably and was able to return home. During most of his stay in hospital he received oxygen (discontinuously) by means of an oxygen tent and parenteral fluid therapy. His skin was always warm, but the temperature was not measured. On six occasions over a period of 24 days, A.V. differences in pH, TCO_2, and pCO_2 were estimated and the results show that the differences were insignificant.

These estimations were very helpful in management and could, in fact, have been performed entirely on peripheral venous blood obtained from the unheated hand. As soon as this point was established venous samples alone were used in the further management of the case.

Case Y was also very ill and had multiple staphylococcal pulmonary abscesses complicating influenza. The illness was very long drawn out but ultimately he recovered completely. At the onset the patient was extremely dyspnœic and the blood analyses showed alveolar hyperventilation (table III). The dyspnœa responded well to continuous oxygen administration.

TABLE III—ARTERIOVENOUS DIFFERENCES IN PLASMA pH, TCO_2, AND pCO_2 IN PATIENT Y WITH STAPHYLOCOCCAL PNEUMONIA

Date (1958)	Skin temp. (°C)	pH		A.V. pH	TCO_2 (mM/1.)		A.V. TCO_2 (mM/1)	pCO_2 (mm.Hg)		A.V. pCO_2 (mm. Hg)
		A.	V.		A.	V.		A.	V.	
April 15	35	7·473	7·467	+0·006	21·8	22·5	−0·7	29·4	30·8	−1·4
April 16	35·5	7·390	7·385	+0·005	22·7	23·2	−0·5	36·8	38·0	−1·2
April 17	35	7·398	7·392	+0·006	23·8	25·5	−1·7	37·9	41·1	−3·2
April 22	35	7·351	7·351	0·000	23·2	23·8	−0·6	41·0	42·0	−1·0
May 2	35	7·452	7·436	+0·016	23·5	23·7	−0·2	33·2	34·7	−1·5

The venous blood was obtained from the back of an unheated hand.

Comparative blood studies, performed on five occasions over a period of 17 days, showed that the A.V. differences in pH, TCO_2, and pCO_2 were negligible. This patient's skin temperature was always 35°C or more.

This case also illustrates the value of venous blood for pH and pCO_2 estimations and shows that when the skin blood-flow is adequate, as indicated by the skin temperature, heating of the limb is not necessary to achieve " arterialisation " of venous blood.

Discussion

The biochemical changes in blood as it passes through the tissues are a function of the rate of blood-flow and the metabolic demands of the cells. Vasodilatation can so increase the blood-flow through the skin of the hand that the blood in the superficial veins is not measurably different from arterial blood in its oxygen saturation, pH, TCO_2 and pCO_2 levels. We have found that if the patient is in bed, and is warm, and the skin temperature over the dorsum of the hand, measured by a mercury thermometer in contact with the skin, is at least 35°C, venous blood obtained without stasis from a superficial vein of the hand will have about the same pH, TCO_2, and pCO_2 level as arterial blood. If the skin temperature is less than that indicated, then a short period of heating of the limb (most conveniently performed by electric pads) should induce the necessary " arterialisation " of venous blood, unless other facts (e.g., gross circulatory insufficiency or intense generalised vasoconstriction) prevent it.

General anæsthesia in the ten patients we studied was associated with spontaneous " arterialisation " of venous blood. While conditions could exist during general anæsthesia which reduce the skin blood-flow sufficiently to produce significant A.V. differences, this should be obvious by a fall of skin temperature. At least one study of pH, TCO_2, and pCO_2 changes during anæsthesia utilising venous blood has been reported (Rollason and Parkes 1957), but no comparison was made with arterial blood.

We feel therefore that, provided the precautions listed above are taken, venous blood may be used for pH, TCO_2, and pCO_2 determinations and that the results will be sufficiently close to the arterial levels for most clinical purposes. Failure to observe the necessary precautions, however, could produce seriously misleading results (see table I).

We have already referred to the work of Meakins and Davies (1919–20) and Goldschmidt and Light (1925) who were able to produce venous blood with the same O_2 saturation as arterial blood by prolonged immersion of the hand and arm in water at 46°C. We studied O_2 saturation in twenty of our patients employing a spectrophotometric method of analysis, and in seven found differences which, although small, nevertheless, because of the shape of the oxyhæmoglobin dissociation curve, rendered the value obtained on venous blood too inexact for clinical use. The method of heating we employed, therefore, and the conditions we have defined for spontaneous " arterialisation " of venous blood, while satisfactory for pH and pCO_2 studies, are unsuitable for O_2 saturation and pO_2 levels. Perhaps if we had used higher temperatures this limitation would have been overcome, and we are now trying to devise a convenient and safe way of achieving increased heating.

Conclusions

It is generally agreed that the assessment of alveolar ventilation in a patient may be difficult without laboratory aids. The most accurate test of this function is the arterial-blood carbon-dioxide tension (pCO_2). The pCO_2 can be derived from two measurements on blood—namely, the blood pH and the plasma total carbon-dioxide content (TCO_2). These estimations are not difficult to perform. Under certain conditions the difference between the arterial and venous pH, TCO_2, and pCO_2 levels, which may normally be quite large, becomes negligible. This state of " arterialisation " of venous blood occurs when the patient is at rest in bed, his skin is warm, and the temperature of the skin over the dorsum of the hand is at least 35°C when measured with a mercury thermometer. The venous blood must be obtained without stasis from a vein over the dorsum of the hand or wrist.

In ten patients operated upon under general anæsthesia venous blood obtained from the back of the hand had virtually the same pH, TCO_2, and pCO_2 levels as arterial blood.

Heating the hand and arm for 15 minutes with electric pads (a common domestic type was used) will also produce " arterialisation " of venous blood.

We believe that these observations will simplify the problem of the management of patients with respiratory and other disorders when blood pH and pCO_2 changes occur, by making it possible to employ venous rather than arterial blood.

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INTRAPERITONEAL TRANSFUSION OF BLOOD IN A CHILD WITH COOLEY'S ANÆMIA

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WITH the perfection of blood-transfusion technique, a growing number of children—many of them with Cooley's anæmia—are having transfusions every few weeks or months. The difficulty of finding adequate veins can become a major challenge to skill and patience, particularly when it has been necessary to carry out extensive cut-downs. In areas where skilled medical attention is less easy to obtain than in this country such a situation could spell disaster for a child. The alternative here recommended is intraperitoneal transfusion.

Though this method has a surprisingly large literature, recently reviewed by Mellish and Wolman (1958), it seems to be seldom used.

Judging by reported cases, the major questions—Is it safe? Does the blood get absorbed unaltered? Does it cause peritonitis or adhesions?—have been answered satisfactorily.

The intraperitoneal injection of clear fluids has, of course, been widely practised in infants and children (Blackfan and Maxcy 1918, Carter 1953), and with certain precautions has proved safe.

As regards blood, experiment has shown that in animals this is absorbed almost exclusively via the lymphatics of the diaphragm. From recent reports (Waite et al. 1956, MacDougall 1958) and from the present case it appears

that in children absorption can be rapid enough to correct any anæmia, provided the patient is not shocked, has a normal peritoneal cavity, and is not losing nor destroying blood at a rate requiring immediate correction. For reasons not yet explained, absorption is occasionally delayed.

At laparotomy after intraperitoneal injections even of whole non-citrated blood (Mengert et al. 1951) the only reaction seen has been some peritoneal injection about a day later. In a child with aplastic anæmia who had a splenectomy after repeated intraperitoneal injections of blood, the peritoneum showed no signs of inflammation (Hedenstedt 1947). This seems to be the only case previously reported in which the peritoneum of a living child was directly inspected after this treatment. MacDougall (1958), however, reported from Nairobi the postmortem findings in seven children, aged 5 months to 2 years, who died of severe infections complicating various types of anæmia, and in whom intraperitoneal transfusions of blood had been done from 24 hours to 21 days previously. Absorption appears to have been rapid, and in none were there any signs of peritoneal reaction. Similar findings are reported by Niesert (1950) concerning two infants. There was, in fact, no evidence that the procedure had been harmful in any way.

Case-history

A.B. was born on July 10, 1957. Like an elder sister, she was found to have thalassæmia major, and she had her first blood-transfusion at 2 months. By the age of 14 months she had had nine transfusions in all, and showed many cut-down scars. There was great difficulty in finding suitable veins, and it had been necessary to resort to syringing blood into the external jugular veins and to carrying out blind cut-downs. No ill effects followed, but an alternative method was clearly needed. In view of MacDougall's report, intraperitoneal transfusion was decided upon.

For practical purposes, the child's blood-volume was calculated as 30 ml. per lb. body-weight (Brines et al. 1941). (Smith 1956, in a report of repeated intravenous transfusions in children with Cooley's anæmia, estimated it at 80 ml. per kg., equalling 36 ml. per lb.) Assuming complete absorption and a "normal" hæmatocrit of the transfused blood (in fact, citrated blood has a lower hæmatocrit, 32–36% according to Smith), the percentage rise of hæmoglobin was expected to be roughly equal to the percentage of blood-volume injected, after excess fluid had been excreted. The last two intravenous transfusions served as controls: in each of these, after the transfusion of approximately 50% of the calculated blood-volume, the hæmoglobin had risen by 49% (4th and 2nd days after transfusion respectively).

The first intraperitoneal injection was on Sept. 27, 1958, and four more—all at the same site—were given before splenectomy was performed on Nov. 13. The patient was no more distressed than by pricking for hæmoglobin estimations. There was no abdominal distension or vomiting: shifting dullness could be elicited after the injections but not 24 hours later. 23–30% of her calculated blood-volume was injected at a time. The blood may well have felt cold, and after one injection her rectal temperature fell by 2°: in future we shall let the delivery tubing rest on towels over a hot-water bottle. There were no febrile reactions: in fact, after the first injection the patient no longer showed the fever she usually had when her hæmoglobin was low. Antibiotic cover was not thought necessary.

Absorption was rather more rapid than was expected. After the first injection (25% of her calculated blood-volume) the hæmoglobin rose by 22% by the 3rd day. Subsequently, after injections of 25% and 30% of her calculated blood-volume, hæmoglobin rises of 21% and 19% respectively were obtained by the 3rd day, and of 25% and 24% by the 5th. On the last two occasions, injections of 25% and of 23% of her calculated blood-volume were followed by rises of only 10% and 7% by the 3rd day and of 18% and 9% by the 5th day respectively; but hæmoglobin readings at this time fluctuated rather more widely than previously, and the inevitable margin of error of the fingerprick method applies to all the estimations quoted.

Assuming the reduced response to be true, several factors might explain it. There was no clinical evidence of increased hæmolysis; nor was there melæna, or evidence of injection into the abdominal wall. Absorption was not delayed, for when the splenectomy was performed hardly any blood remained in the peritoneal cavity. But the last injection was given at a hæmoglobin level higher than previously, so as to prepare the child for operation, and estimations of blood and plasma volumes in such circumstances at different degrees of anæmia might prove instructive. There were no significant weight changes.

Our findings suggest not only that absorption was quite rapid but also that, as in the case of Waite et al. (1956), it was almost complete. 24 hours after the intraperitoneal injection blood-films showed an increased proportion of normal-appearing red cells (figs. 1 and 2), this increase being most obvious when the pre-injection hæmoglobin level was low. As expected, fœtal hæmoglobin estimations showed a dilution effect, and the values remained lower than previously—probably because of depression of marrow by the repeated transfusions (Smith et al. 1955).

Hæmoglobin values fell at the same rate after intraperitoneal transfusion as after intravenous transfusion, which agrees with previous evidence (Hedenstedt 1947, Pritchard and Adams 1957), though Mellish and Wolman (1958) point out that for children there are no data from the use of radio-tagged cells. (We refrained from using this method because of the possible effects of a radioactive pool round the ovaries, but poor prognosis for these patients at the present time could be held to make this risk unimportant.)

When the abdomen was opened for splenectomy, only a little bloodstained fluid was found in the peritoneal cavity. The greater omentum was free and appeared normal. There were no adhesions, and the serous coat was smooth and shiny except over the convex surface of the much-enlarged spleen. The peritoneal blood-vessels were a little prominent. Five intraperitoneal injections of blood (each of 200–250 ml.) had been given between 47 and 6 days before the operation.

Conclusion

If the efficacy and safety of intraperitoneal transfusion can be confirmed, it will deserve wider use. The advantages claimed for it, and borne out in our case, are that it can be done whatever the scarcity of veins; that it leaves

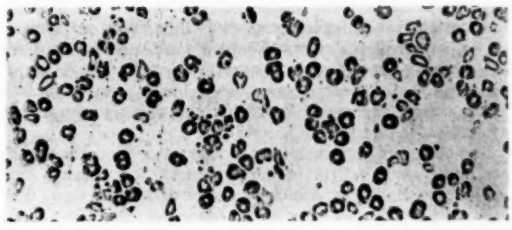

Fig. 1—Appearance of peripheral blood before transfusion (Hb 21%).

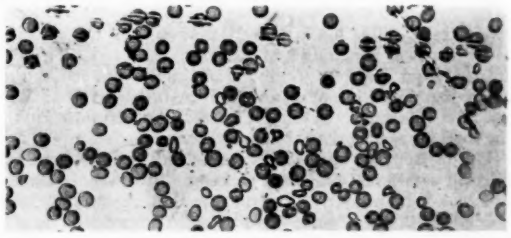

Fig. 2—Appearance of peripheral blood 24 hours after intraperitoneal transfusion (Hb 30%).

no scars; that it can be repeated as required; that it is effective and harmless; and that it causes no greater discomfort than does cut-down intravenous technique with splinting. (In fact, it takes a shorter time, and no restraint is imposed afterwards.) A further advantage is that the technique of its use in young children can be easily acquired.

Summary

A child with thalassæmia major was given intraperitoneal transfusions of citrated whole blood on five occasions between the ages of 14 and 15 1/3 months. 23–30% of her calculated blood-volume was given at each transfusion.

On three out of five occasions the effect of these transfusions was highly satisfactory. By the 3rd day it was comparable to the effect of intravenous transfusion of the same amount of blood. Possible reasons for the reduced hæmoglobin response on the last two occasions are discussed.

There were no undesirable side-effects, nor did there appear to be undue discomfort. At laparotomy for splenectomy, 47 days after the first transfusion and 6 days after the last, the peritoneum was found normal. Absorption of the blood had been almost complete.

In children where there is difficulty in finding veins suitable for injection, intraperitoneal transfusion may be the method of choice. It deserves further and extensive study.

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Appendix

Technique.—The patient was sedated as for intravenous transfusion. The abdomen was exposed, the skin cleaned with spirit and iodine, and 1% procaine injected as local anæsthetic. The injection site chosen was a point on the outer border of the right rectus abdominis muscle, a little below the umbilicus. A 20 ml. syringe and three-way tap was used. Two drip sets, one containing citrated whole blood (routinely grouped and cross-matched) and the other normal saline, were connected to one socket through a two-way tap; a waste tube and delivery tube were connected to the other two sockets. A slightly blunted large lumbar-puncture needle was connected to the delivery tube. The system was filled with saline, to prevent any intramuscular injection of blood.

The abdomen was examined to make sure that the bladder was empty, and to locate the border of the spleen, which reached the umbilicus. Pinching up the abdominal wall (Waite et al. 1956) failed to include the muscular layer, but helped when piercing the skin and subcutaneous tissues. The deeper layers were then pierced, pressure being exerted on the plunger of the syringe so that it moved forwards as soon as the abdomen was entered. This has a theoretical advantage in that the jet of saline makes penetration of the bowel less likely. This is in any case an unlikely complication, unless there is tight abdominal distension or adhesion of the bowel near the site of injection. On entry, the hilt of the needle was depressed so that the shaft lay against the parietal peritoneum.

Up to 30% of the child's calculated blood-volume was injected at a time. Once the technique had become familiar, this took half an hour. After the injection, the foot of the cot was raised 12 in., because this may assist absorption (Courtice and Steinbeck 1951). For the next 24 hours the stools were watched for melæna.

SUBACUTE INTESTINAL OBSTRUCTION AS A CAUSE OF DIARRHŒA

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(NORTH HERTS AND SOUTH BEDS AND LISTER HOSPITALS)

THIS paper draws attention to a clinical picture with all the features of acute intestinal obstruction *but*, in place of absolute constipation, a distressing and copious diarrhœa. This syndrome is the result of an incomplete intestinal obstruction.

The condition is important for several reasons. Severe fluid and electrolytic disturbance may follow the diarrhœa, vomiting, and dilatation of the bowel. The condition may last for many weeks, during which the loss of fluid and electrolytes is difficult to control; and early operation may be necessary to avoid the dangers of these prolonged physiological changes. Diarrhœa after an operation may be taken as evidence of a patent bowel lumen; paradoxically, however, it may be caused by partial intestinal obstruction.

Finally, diarrhœa in a patient without pyrexia, or a stool containing pathogenic organisms, should arouse suspicion of an obstructing carcinoma, stricture, fæcal impaction, or even a large innocent tumour.

Case-reports

Case 1.—A boy, aged 10, was admitted to hospital with an eight-day history of central abdominal pain, colicky at times, with bouts of vomiting and diarrhœa. He looked ill and was much dehydrated. Temperature was 101 F, pulse 120. The chest was clear. The abdomen was distended and tender (particularly in the midline below the umbilicus), and bowel sounds were unusually frequent and noisy. Rectal examination caused pain, but no mass or particular tenderness was noted.

The vomiting stopped after admission, but the pain and copious diarrhœa continued. A plain X-ray showed dilated loops of small bowel. The provisional diagnosis was incomplete obstruction, probably due to an inflamed Meckel's diverticulum with an adherent loop of small bowel.

During the phase of resuscitation the bowel sounds disappeared and the diarrhœa ceased; ileus had supervened. Laparotomy was nevertheless carried out through a right paramedian incision. Distended loops of small bowel were found leading down to a kinked loop adherent to an inflamed appendix whose tip overlay the sacral promontory. The bowel was released and the appendix removed.

In the postoperative phase parenteral fluids, gastric suction, and antibiotics were used. Bowel sounds started after three days and normal bowel function followed.

Case 2.—A woman, aged 40, was admitted to Skipton General Hospital in October, 1952, under the care of Mr. E. T. McCartney. Two months before admission she had had an operation for strangulated hernia in a Liverpool hospital. A month later she began to have attacks of colicky abdominal pain lasting for about an hour, and often ending by vomiting dark-brown fluid. These attacks were accompanied by diarrhœa, distension, and a noisy abdomen, and occurred at intervals of approximately ten days. The stools examined were normal.

Her general condition was good, and a cystic mass, tender on palpation, was discovered in the left iliac fossa. Operation revealed distended loops of small bowel and an obstruction caused by a loop of bowel that had been caught in the neck of the repaired femoral hernial orifice, where the lumen had become grossly narrowed. The loop was excised and a side-to-side ileo-ileostomy performed. There were no other abnormalities in the abdomen.

She progressed well after the operation and has had no further attacks of vomiting, pain, or diarrhœa.

Case 3.—A boy, 10 months old, was admitted to the Lister Hospital under Dr. C. G. Fagg. His birth-weight was 8 lb. The child had melæna up to the third day, and after this was well until the fourth week. Vomiting then began and continued. A little weight only was gained in the first three months. Breast feeding was stopped at the fourth month, because it was thought not to be agreeing with him.

Improvement followed for two weeks and his weight went up to 10 lb. 15 oz. Diarrhœa began a week later and the motions were yellow, bulky, and streaked with blood. During his stay in hospital this diarrhœa continued for five weeks. The stools contained undigested food, and he failed to gain weight. The abdomen was, and remained, distended.

He was referred to Mr. D. Levi and admitted to Westminster Children's Hospital. He was observed for twenty-four hours and his condition deteriorated. Complete constipation ensued and laparotomy was undertaken.

Through a transverse incision a considerable quantity of gas was found in the peritoneal cavity, and a grossly distended loop of bowel presented. The cæcum and terminal ileum were collapsed. The obstruction was found 8 in. from the ileocæcal valve, where there was almost complete atresia. From the proximal side of the atretic segment a thick band passed upwards to the hepatic flexure. A volvulus had occurred around this band. The central part of the band was divided and the volvulus relieved. To restore the continuity of the bowel the atretic segment was by-passed by a side-to-side entero-anastomosis. Postoperatively the infant made a satisfactory recovery and has continued to thrive. Bowel actions have returned to normal frequency and appearance.

Case 4.—A woman of 75 was admitted complaining of loss of weight, variation in bowel habit, anorexia, and attacks of colicky upper abdominal pain. The bowels had not acted for the previous five days. Flatus had not been passed for two days.

She was thin and cachectic, and there was evidence of intestinal obstruction. The abdomen was distended and tender, and an increase in the pitch and frequency of the bowel sounds was heard. The rectum was empty. Successive enemas failed to correct the obstruction so laparotomy was decided upon. Local anæsthesia was used to establish a transverse colostomy for an obstructing growth of the transverse colon.

Two days later the colostomy acted, but from the next day it overacted and copious outpouring of fluid fæces followed. The skin around the colostomy became burned and the patient grew dehydrated. Supplementary parenteral fluids were needed. Electrolyte levels were checked and maintained throughout. The passage of methylene-blue from mouth to colostomy was recorded as two and a half hours. Stools examined on two occasions contained no pathogenic organism or other abnormality. Further excoriation developed, so a tube was inserted into the colostomy and continuous suction maintained. This overactivity persisted for twenty-nine days. In view of the progressive deterioration of the patient's general condition, operation was undertaken: this consisted of the excision of the colostomy, the growth in the left half of the transverse colon, mesocolon, including middle colic vessels, most of the ascending colon, and an end-to-end anastomosis of ascending colon to descending colon was established. The appendix was removed. A loop of small bowel was found firmly adherent to the inferior surface of the emerging colostomy, and its freeing required sharp dissection. This was considered to be the cause of the incomplete obstruction.

After the second operation the patient improved, but overactivity soon recurred, and liquid stools poured from the rectum for a further six days. No pathogenic organism or other abnormality was found in the stools. Electrolyte levels were constantly watched and the patient was encouraged to drink half-strength saline flavoured with orange juice. Methylene-blue administered orally came through the rectum in four and a half hours. Again it was decided that the patient was losing ground so a further laparotomy was performed. Two possible causes were discovered: a loop of bowel had become adherent to the under surface of the abdominal wall and the loop of small bowel previously dissected off the colostomy was narrowed. The narrowed portion was incised in the long axis of the bowel and then closed transversely to enlarge the lumen. After this the patient slowly returned to normal and was discharged from hospital.

She was last seen in the outpatient department in October, 1957. Her bowels were then acting once or twice a day and the stools were " formed ".

Discussion

" Peristalsis is a reflex mediated by the myenteric plexus of Auerbach and evoked by stimulation of the nerve endings in the wall of the gut. A rising intra-luminal tension provides a very effective stimulus. The response is first increased contractions and possibly waves of reverse peristalsis and finally, when gross stretching has occurred, inhibition of peristalsis and passive dilatation."—Rodney Smith (1948).

Peristaltic activity varies with a rise in intraluminal tension. It may cease, as in ileus, or overact in an effort to overcome the obstruction. Above a partial or incomplete obstruction the bowel distends and overacts. This overactivity may persist, resulting in diarrhœa and other effects. The speed of the transit of the bowel content is increased and the behaviour of the bowel may best be described as " intestinal hurry ".

The above case-reports illustrate this type of activity, caused by a partial mechanical obstruction of the lumen, and these patients have certain clinical features in common.

Diarrhœa.—The stools are unformed because there has been insufficient time for water reabsorption in the colon. The heightened activity may be measured by the charcoal or methylene-blue tests (2-grain tablets taken by mouth appear in the fæces, and the time taken to pass is measured). In the cases recorded here this time has been short—as rapid as four hours.

Diarrhœa may be due solely to the failure of the colon to absorb water. Similar obstructive phases, however, are seen in patients without colons—that is, with ileostomies—a condition which has been termed ileostomy dysfunction (Warren and McKittrick 1951). The distressing attacks of copious diarrhœa in these patients are cured by gentle dilatation of the ileostomy by the employment of a soft rubber tube. The hold-up occurs as the ileum traverses the abdominal wall and the tightness can be experienced by introducing a finger through the ileostomy.

Stools are unformed and large. They have resembled in colour and consistence fluid obtained through a Ryle's tube from the stomach or upper reaches of the bowel.

Distension is present, the amount depending on the level of the obstruction.

Auscultation is a most useful aid to diagnosis, the exaggerated bowel activity being easily recognised. The sounds are noisier, more frequent, and have a high-pitched " tinkling " note.

General signs.—The patient shows evidence of loss of water and salt, a dry tongue, inelastic skin, low blood-pressure, and possibly a rising pulse. As the partial obstruction persists, fluid and electrolytes are lost into the lumen of the dilating bowel. Vomiting and diarrhœa cause further losses. Serological examination may reveal falling electrolyte levels. The chloride level falls in the urine.

Radiography of the abdomen.—" A localised increase in peristaltic activity may be seen " (Martin and Friedell 1952). " Vigorous peristalsis is a definite sign " (Duncan White 1936). Dilated loops of bowel may be seen in a straight X-ray.

Pain.—Central colicky pain may accompany the attacks of diarrhœa.

Changes of bowel habit.—Ransom (1939) reported such changes in 50% of a series of patients with carcinoma of the right colon.

Aylett (1954) reported similar changes in 90% of a series of carcinomas of the left side of the colon. Alternating constipation and diarrhœa is thought to indicate

chronic obstruction of the large bowel. The attacks of diarrhœa probably denote phases of heightened peristaltic activity due to incomplete obstruction. Cessation of the diarrhœa may be the result of discharge of necrotic tissue at the centre of an annular carcinoma, which would enlarge the lumen, or a reduction in bowel distension.

Summary

In 4 cases of incomplete obstruction, diarrhœa, distension, and heightened bowel activity were common features. Oral methylene-blue was useful as a test of this intestinal overactivity.

Diarrhœa should not be taken as evidence of a normal bowel lumen; on the contrary, it should rouse suspicion of an incomplete obstruction.

I am indebted to Mr. G. T. McCartney, Dr. C. G. Fagg, and Mr. D. Levi for permission to publish these reports; and I wish to thank Mr. H. E. Lockhart-Mummery in particular for his interest, advice, and support on this subject.

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Preliminary Communication

INFLUENCE OF CALCIUM IONS ON VITAMIN-B_{12} ABSORPTION IN STEATORRHŒA AND PERNICIOUS ANÆMIA

Gräsbeck and Nyberg [1] have shown that calcium ions are probably necessary for the intestinal absorption of vitamin B_{12}—at any rate when this is given in physiological quantities. This conclusion was based on the finding that, in normal subjects, ethylenediamine tetra-acetate (EDTA) by mouth caused a notable decrease in the urinary-radioactivity values obtained in the Schilling test, and that this effect was avoided when calcium lactate was given with the EDTA and the radiovitamin. The study was inspired by Herbert's finding [2] that, in vitro, intrinsic-factor preparations do not stimulate the uptake of vitamin B_{12} by liver slices unless calcium ions are present.

Gräsbeck and Nyberg's observations [1] suggested that the impaired vitamin-B_{12} absorption in steatorrhœa might be due to the lack of calcium ions. (Removal of these ions by the fatty acids in the form of insoluble calcium soaps is thought to be responsible for the poor calcium absorption in steatorrhœa.[3]) Our data show (see table) that, in some patients with steatorrhœa, calcium by mouth increases the Schilling-test value, and this supports the hypothesis that lack of calcium ions contributes to the inefficient vitamin-B_{12} absorption in this condition. On the other hand, calcium administration did not influence the vitamin-B_{12} absorption in addisonian pernicious anæmia.

METHOD

Our experimental technique was very simple. The patients were subjected to two Schilling tests at an interval of about a week. The oral dose was 1 μg. of ^{60}Co-labelled vitamin B_{12}, the 1 mg. flushing dose was injected 90 minutes after the oral dose, and the urine was collected for 24 hours. In one test calcium lactate was administered also, half the dose being given 30 minutes before the radiovitamin, and the rest simultaneously. The dose of calcium lactate was 7 g. for adults and 2 g. for infants.

THE EFFECT OF ORAL CALCIUM ADMINISTRATION ON THE SCHILLING-TEST VALUES OF PATIENTS WITH STEATORRHŒA AND PERNICIOUS ANÆMIA

Case no.	Clinical data	Schilling test (urinary radioactivity as % of oral dose)	
		Usual test	With calcium
1	Idiopathic steatorrhœa, female, aged 62 (A, H)	0·3	20·1
2	Idiopathic steatorrhœa, female, 51 (H)	3·2	7·5
3	Idiopathic? steatorrhœa, cirrhosis, male, 56 (A, H)	0	0·3
4	Latent steatorrhœa, male, 54 (A)	0·1	4·4
5	Cœliac disease, male, 1 yr.	1·5	2·4
6	Cœliac disease, male, 1 yr.	5·5	8·4
7–12	Pernicious anæmia, 2 males and 4 females, aged 59–70	0–1·7	0–1·7

A = megaloblastic anæmia responding to vitamin B_{12}; H = hypocalcæmic signs.

RESULTS AND CONCLUSIONS

The results are shown in the table. In pernicious anæmia calcium had no definite effect. On the other hand, in steatorrhœa, administration of calcium clearly increased the urinary radioactivity in four of the six patients, though in the other two only a slight (and presumably insignificant) increase was noted. Thus it seems that a deficiency of free calcium ions in the intestine is one of the causes of the poor vitamin-B_{12} absorption in steatorrhœa. But the weak response in two cases suggests that lack of calcium ions is not the sole cause of the impaired B_{12} absorption in these conditions. Other pathophysiological mechanisms causing poor vitamin-B_{12} absorption with resulting vitamin deficiency may include, for instance, decreased production of intrinsic factor (achlorhydria is common), rapid passage of the chyme (which might hamper the intestinal reabsorption [4] of biliary B_{12}), a decrease in the absorptive area (with a possible concomitant loss of intramural-B_{12}-acceptor [5]), envelopment of the vitamin by fat droplets in the chyme, abnormal microbial flora, and various combinations of these factors. By performing modified absorption tests in which calcium, intrinsic factor, antibiotics, &c., are given simultaneously with the radioactive vitamin, it may be possible to elucidate the role of these factors in an individual case.

Because many enzyme systems need inorganic ions as activators, it is possible that analogous mechanisms might hamper the absorption of other nutrients as well. As regards the mechanism whereby calcium participates in the absorption of vitamin B_{12}, it is worth mentioning that Nyberg and Gräsbeck, using dialysis techniques, have recently observed that EDTA influences the binding of B_{12} to intrinsic-factor preparations in vitro. These results will be published shortly.

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New Inventions

A NIGHT BOOT

WE have recently introduced a modification of the Denis Browne night boot which has proved very satisfactory. It is used in toddlers with talipes equinovarus, when the foot can be passively corrected without difficulty but tends to relapse as soon as it is left free.

The boots are made with the tracing of the feet reversed (fig. 1) so as to correct the adduction deformity. The outer side of the boot is wedged by $^1/_4$ in. to correct inversion, and sockets (rectangular in cross-section) are inserted into the heels below the wedge (fig. 2). A right-angled bar is slotted into the sockets when the child is in bed, to keep the legs externally rotated and the feet aligned in slight eversion (fig. 3).

Fig. 1.

The advantages of this splint are (1) the absence of nuts, which are continually undone by the children; and (2) the fact that the same shoe is used for running about and as a night splint.

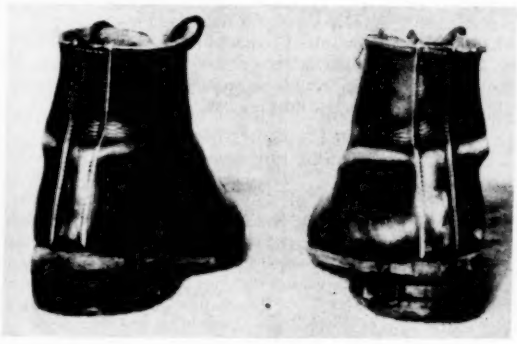
Fig. 2.

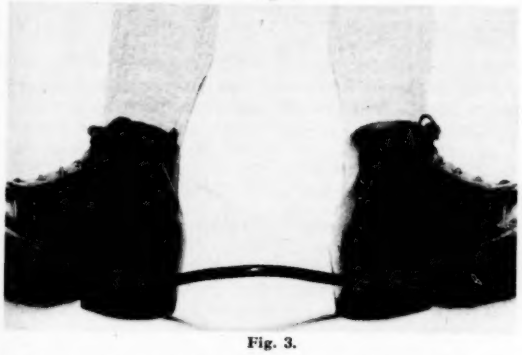
Fig. 3.

I should like to express my thanks to Mr. W. Thompson of Remploy Ltd., Chesterfield, who are making this splint for us.

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Reviews of Books

Surgery of the Sympathetic Nervous System

3rd ed. Sir JAMES PATERSON ROSS, LL.D., M.S., F.R.C.S., director of the surgical professorial unit, St. Bartholomew's Hospital, London. London: Baillière, Tindall, & Cox. 1958. Pp. 170. 35s.

THE wave of enthusiasm for extirpation of parts of the sympathetic nervous system with the hope of favourably influencing all sorts of conditions from ununited fractures to retinitis pigmentosa has long subsided, and relatively few indications for sympathectomy remain today. The third edition of this book, which appeared first in 1933 under the authorship of the late Prof. George Gask and Sir James Paterson Ross, is an account of the experience of sympathectomies gained in the surgical unit at St. Bartholomew's Hospital. Sir James says it has been necessary to rewrite the greater part of the book; and it would have been surprising had it not been so, for there must be few branches of surgery which have undergone such changes during the past few years. He remarks that in its early days sympathectomy had to be regarded as a long-term experiment in human physiology. Now that we are able to evaluate the results it seems that its indications are limited, and for the most part the operation has little to offer in the many conditions for which it has been tried. The thoracolumbar parts of the system alone are dealt with, and, after an introduction, the six chapters are concerned with anatomy and physiology, and then sympathectomy for peripheral vascular disorders, arterial hypertension, hyperhidrosis, causalgia, and visceral pain. This story of the decline of sympathectomy, interspersed as it is with brief glimpses of the historical background of the operation and personal experiences, makes interesting reading, especially if it can be examined in conjunction with the first edition. The book, which is well printed and illustrated, gives a precise account of the operations now performed on the sympathetic system and what may be expected from them, by an author whose experience is unrivalled.

The ABO Blood Groups

Comprehensive Tables and Maps of World Distribution. A. E. MOURANT, D.M., M.R.C.P., director, Medical Research Council Blood Group Reference Laboratory, Lister Institute of Preventive Medicine, London; ADA C. KOPEC, D. ÈS SC., statistician, Nuffield Blood Group Centre; KAZIMIERA DOMANIEWSKA-SOBCZAK, M.A., A.L.A., librarian, Nuffield Blood Group Centre. Oxford: Blackwell Scientific Publications. 1958. Pp. 276. 42s.

THIS formidable volume is "occasional publication no. 13" of the Royal Anthropological Institute; and the Nuffield Foundation, the Royal Society of London, and the Wenner-Gren Foundation of New York have given financial support to its preparation and publication. Most of the book is taken up with comprehensive tables setting out available reliable data on the distribution of blood-groups in every country in the world. The size of the sample and the actual numbers in each group are given as well as the percentage distributions. Calculations of gene frequencies are included. Most of the data deal with ABO blood-groups without distinction between A_1 and A_2, but a smaller table gives data about A_1A_2BO groups. There are 1056 references and finally 6 maps—3 of distribution of blood-groups A, B, and O in Europe, and 3 of the same distribution in the "aboriginal populations of the world".

The book is clearly indispensable to anyone working with blood-groups, and every reference library in the world will need a copy. The non-specialist may be awed by the incredible amount of work that has been done, but he can find any number of odd facts to stimulate his imagination. Why should people with Welsh surnames who live in the Teifi basin in South Wales have less than 40% of group O, while those in the Clwyd valley and the Denbigh coastal plain in North Wales have 56·8% group O. Inverness West boasts 59·3% group O, but Dundee only 43·5%. Why does the sample of soldiers at Astrakhan include autochthones? And the man who investigated "old city families" at Meknès in Morocco must have had an entertaining time.

Human Infertility

C. LEE BUXTON, M.D., MED.SC.D., professor and chairman, department of obstetrics and gynecology, Yale University School of Medicine; ANNA L. SOUTHAM, M.D., assistant professor of obstetrics and gynecology, College of Physicians and Surgeons, Columbia University, and director of Sloane Hospital Infertility Clinic, New York. London: Cassell. 1958. Pp. 229. 57*s*. 6*d*

THE authors say they have attempted to be " candidly realistic " in presenting their views on human infertility, " its prevalence, its implications to both society and the individuals involved, its diagnosis, its treatment, and, within our experience, the results of treatment ". These aspects of infertility are dealt with at length. There is a valuable section on consideration of the couple as a unit, in which stress is rightly laid on the history as perhaps the most important of all investigations. The problem is not the same in every case, and time spent on the history will help to show how each problem may best be studied further. This refreshing idea is much to be preferred to a rigid plan in which a series of investigations are performed in a fixed order.

The various investigations available are discussed very fully in sections on the hormonal, cervical, tubal, and psychological factors in infertility. There is a clear and interesting account of endometrial interpretation by the late Earl T. Engle and a section on the gynæcologist's responsibility in male infertility. Investigation and treatment in a large series of the authors' cases are described.

Surprisingly there is little mention of the problem of pelvic tuberculosis in infertility, and a more detailed account of the results of tubal plastic operations would have been welcome. The only serious defect of the book is its style: long and complex sentences have to be read several times before their meaning is at all clear. Bizarre words and phrases are so puzzling that they may hide the meaning of a whole passage. Colourful though much of the book is, it would be better written in plain English.

The Sudan Medical Service: an Experiment in Social Medicine

H. C. SQUIRES, C.M.G., D.M., F.R.C.P. London: Heineman Medical Books. 1958. Pp. 138. 15*s*.

THE Sudan Medical Service was formed in 1904, and this book traces its growth during the British-Egyptian and British periods until 1951. In a foreword, Dr. Ali Bedri, the first Minister of Health under British rule, speaks appreciatively of British doctors' service to the Sudan and of Dr. Squires as a clinical teacher.

After 26 years in the Sudan and a further 21 in the service of the Sudan Government in London, Dr. Squires is well qualified to describe the Service almost from its beginning. Its small size was determined partly by financial restrictions and partly by the insistence on quality by the selectors of candidates. The revenue of the country rose from £35,000 in 1898 to £35,000,000 in 1955—a thousandfold increase in fifty-six years. In the days of financial stringency all officials, medical and civil, had to undertake the work of many men, an administrative custom that persisted long. The early members of the Service were hand-picked from the young and outstanding medical graduates, and their high quality is thus not surprising, especially since they were chosen for quality rather than by any rigid criteria of qualification. The proportion was therefore high of men who had or who later obtained higher diplomas in medicine and surgery.

At the start a good deal of the actual medical work seems to have been done by Syrian and Egyptian doctors, to whose devoted application Dr. Squires pays tribute, and they staffed the hospitals that were established. The British members of the Service, according to their bents and abilities, became clinicians, sanitarians, administrators. Most included all these capacities at once in their work, and a few also became research-workers of distinction. They were designated " medical inspectors ", a title that still persists in the Sudanised Service and that is held by doctors who are in charge of small hospitals and also are responsible for the health of large areas. The British doctors of those early days included names to be later widely known.

Then follow accounts of the work done in dealing with epidemics of sleeping-sickness, malaria, cerebrospinal meningitis, and relapsing fever. Under endemic disease are linked kala-azar, leprosy, and tuberculosis; but Madura mycosis is not mentioned, which is surprising because this disease is a scourge in the Northern Sudan and shares with tuberculosis the first place in importance as a surgical disease. Unhappily it does not share with tuberculosis a sensitivity to known drugs or antibiotics. Thus, excision, sometimes mutilating, and amputation, are the only available treatments and even these are not always applicable.

The expansion of the Service from its small beginnings continued as the finances of the country increased—an improvement largely the result of widespread cotton-growing with irrigation. The shortage of doctors remained great, but was eased by the training of some of the best of the male nurses as medical assistants. The medical assistants do much of the work usually done by doctors, and they are one of the most impressive features of the Sudan Medical Service. They can recognise parasites in stools, urine, and smears from lymph-gland punctures, and have been known to cope single-handed with minor epidemics.

The wisdom of Lord Kitchener led to the foundation of the Gordon Memorial College, which undertook the education of Sudanese and is now the University of Khartoum, and later to the foundation of the Kitchener School of Medicine, now the university's medical faculty. Since 1928 there has been a stream of new Sudanese entrants to the Service, now amounting to about twenty doctors annually and the number is increasing. Dr. Squires refers to another scheme to meet medical needs, the successful and now famous school of the Misses Wolff for training illiterate women as midwives. The account of the nursing service is sketchy and includes little more than the names and short biographies of past sisters and matrons.

The book is seldom critical, and to some readers this may seem less than the deserts of the men who built up a service of which Britain has reason to be proud, both for what it was and for what it now is in Sudanese hands.

Identity (World Federation of Mental Health Introductory Study no. 1. London: H. K. Lewis. 1958. Pp. 46. 5*s*.).—The scientific committee of the Federation was formed to develop a body of knowledge and to provide more solid conceptual foundations for the work of the Federation. This is its first study project, and the topic of " identity " was chosen, as the foreword says, because it bears not only on such ideas as " positive mental health " but also on the practical matters of world citizenship, technical-assistance programmes, population movement, and change of class. After attempts at definition, identity is discussed briefly in fourteen sections under headings including its development; empathy; identification with others; identity and group membership; cultural factors; hierarchy of identities; unusual and extreme forms; and breakdown of identity. A concluding section suggests further projects for study. Although the treatment is introductory it is wide enough to stimulate the reader to thought and further reading. It is a pity that the authorities cited could not have been listed with full details of their relevant publications; but the booklet is excellent value and full of meat.

A Synopsis of Hygiene (Jameson and Parkinson) (11th ed. London: J. & A. Churchill. 1958. Pp. 694. 60*s*.).—There cannot be much wrong with a book which reaches an eleventh edition within forty years. " Jameson and Parkinson " is the vade-mecum of all who have any concern with the public health. It would be easy for the expert to complain of small omissions or errors of emphasis in his own department; but Dr. Llywelyn Roberts and Dr. Kathleen Shaw, the editors, support all the newer additions to knowledge by references to original sources, chosen very wisely from journals which are likely to be easily available. As we learn more, our books must get larger: in this case the enlargement is an advantage. New type and better paper have made this edition better looking and easier to read than earlier ones.

THE LANCET

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Fifty Years of the School Health Service

"IF from our labours some of the blind see, the deaf hear, the halt attend school, and all have the gospel of health preached to them, the medical supervision of schools cannot but affect the health of the next generation to a greater degree than any other preventive measure with which I am acquainted."

So wrote MEREDITH RICHARDS, medical officer of health for Croydon, just before the School Medical Service started in 1907. Unquestionably the service did improve the health of the next generation, and had RICHARDS been able to read Sir JOHN CHARLES' review of the first fifty years,[1] and compare the photographs of Croydon twelve-year-olds in 1936 and 1956, he would have been more than satisfied with his prediction.

Compulsory elementary education was introduced in England in 1870, but no systematic provision for the physical needs of schoolchildren was made until this century. Though the primary object of the Education (Provision of Meals) Act, 1906, and the Education (Administrative Provisions) Act, 1907, was to fit the child to receive education, "this new legislation", said the Board of Education, "aims not merely at a physical or anthropometric survey of a record of defects disclosed by medical inspection, but at the physical improvement, and as a natural corollary, the mental and moral improvement of coming generations". During the formative stages of the great project, it was indeed fortunate that ROBERT MORANT, as secretary of the board, and GEORGE NEWMAN as chief medical officer, were in partnership; and it is noteworthy that in its fifty years there have been only four chief medical officers—Sir GEORGE NEWMAN, Sir ARTHUR MACNALTY, Sir WILSON JAMESON, and Sir JOHN CHARLES. To show how much the circumstances of children have changed under their auspices we need go no further than the mortality figures: in the first decade of this century deaths per thousand living numbered 3·6 in the 5–10 age-group and 2·1 at 10–15; in the third decade the figures had fallen to 2·4 and 1·6; but in 1957 they were only 0·4 and 0·37. Astonishingly, the number of deaths among children fell from 2966 per million in 1906 to 406 per million in 1955.[2] To this improvement the School Health Services have contributed a system of ascertainment which was badly needed and an approach which, at its best, unites the good endeavours of the child, parent, teacher, nurse, and family doctor. For a long time, unfortunately, relations between the school medical staff and the general practitioner were none too cordial, but of late they have steadily improved through better understanding.

How far the system of ascertainment is adequate is a matter of opinion: MORRIS,[3] for example, has expressed surprise that otitis media was found at school inspections in only 7·6 per 1000 children in 1951, whereas in 1954–55 no fewer than 32 per 1000 were rejected for National Service because of this condition. But the task is certainly enormous. Thus in 1957, out of some $6\frac{1}{4}$ million schoolchildren, over 2 million had periodic or routine examinations and a million were re-examined, while another million or so had a special medical examination. Discussing the value of the periodic examination, the report asks that variations in the technique of selection should be considered. It also provides a great deal of information, which is carefully annotated. On the dental side, the school services have done a great deal to improve health; but, though it is a far cry from the first dental clinic in Cambridge, the services of today are still lamentably undermanned. From the chapters one can see something of how the development of special provisions has helped in the care of children with defective vision, hearing, or speech, or physical handicaps; the educationally subnormal, the maladjusted, and the epileptic; and the diabetic and delicate.

Where, then, will the School Health Service go from here? "It would be strange after 50 years", writes Sir JOHN, "if there were to be no need to alter techniques." Now that there is a comprehensive National Health Service, should there be any need for a school service? Ideally, perhaps not. But the fact remains that, unlike the N.H.S.—so far—the School Health Service is genuinely preventive both in concept and in practice; the job it is assigned is to supervise children in school and to help the physically and mentally handicapped; and in doing that job it can serve as a link between home, school, and the specialist branches of the N.H.S. Even within the past decade, the work of school doctors and nurses has been changing fast, and the service will need to adapt itself continuously and become more selective in its aims. Does it pay enough attention to the difficulties of the individual child, to health education and the teaching of healthy living, to immunisation, and above all perhaps to mental and emotional handicaps and the problems of delinquency? An appendix to the report contains an encouraging list of special investigations by school doctors and others, showing how in some local-authority areas the school health services promote research and—even more important—act on its findings.

How Common is Sex Reversal?

SINCE so many patients with so many different syndromes have been proved in the past few years to have nuclear sex at variance with their apparent sex, and estimates of the frequency of such sex reversal have been steadily rising, it has become an obvious necessity to determine the true incidence by nuclear-sexing a large random sample of apparently normal people. Obvious, but daunting: even by the oral mucosal smear

1. The Health of the School Child: Fifty Years of the School Health Service. Report of the Chief Medical Officer of the Ministry of Education for 1956 and 1957. London: H.M. Stationery Office. Pp. 220. 10*s*. 6*d*.
2. Thomson, D. *Mon. Bull. Min. Hlth publ. Hlth lab. Serv.* July, 1957, p. 124; cited in the report.
3. Morris, J. N. See *Lancet*, 1957, i, 41.

method [1] the labour involved in a large survey is very great. Nevertheless, Dr. KEITH MOORE, whose article appears on p. 217 of this issue, has now completed a survey of all the 3715 babies born in Winnipeg General Hospital in one year, and has found this sufficient to produce most significant results. All the 1804 apparent females were confirmed as genetic females. Of the 1911 apparent males, however, 5 proved to have female nuclear sex. Apparently, therefore (as had been suspected), sex reversal is not symmetrical—that is to say, female-to-masculine sex reversal is much commoner than male-to-feminine —and incidentally the difference is enough to account for a small but significant fraction of the differential sex ratio at birth. While completely feminised males (Turner's syndrome and related gonadal dysgeneses, and testicular feminisation) are rare enough to be completely absent from MOORE's series, completely masculinised genetic females are almost common, forming something like 1 in 400 of the masculine population.

Nearly all such cases must be examples of chromatin-positive Klinefelter's syndrome. Since the first cases were described less than three years ago,[2] substantial series of cases have been reported from several centres.[3–7] High incidences of the condition have been demonstrated in patients attending male infertility clinics [8 9] and in mental defectives.[10 11] As Dr. FERGUSON-SMITH points out this week (p. 219) combination of the various surveys made in Glasgow shows that the incidence in that city cannot be less than 1 in 3000, and it is probably a good deal higher. PRADER et al.[11] believed that the incidence in Zürich was at least 1 in 1000. It is possible to deduce an estimate very near MOORE's from other sources. Combination of CAMPBELL's [12] estimate that 12% of married couples are infertile with DAVIDSON's [13] that the husband is azoospermic in 8% of such couples investigated suggests that some 1% of men produce no spermatozoa. The figures of FERGUSON-SMITH et al.[9] indicate that 17% of azoospermics are chromatin-positive. This is 0·17% (or 1 in 600) of all men; and if we allow for the undetermined (but not negligible) number who produce some spermatozoa, we end up with something not much less than MOORE's 1 in 400. This is a remarkable finding, even if it is only approximately correct. There must be one or two genetic females in every battalion of the British Army, and a few such cases on nearly every general practitioner's list.

We may have to abandon some attractive hypotheses of the origin of sex-reversed Klinefelter's syndrome. Most people will be loth to forgo the idea of some kind of genetic background. A very few pairs of affected brothers have been recorded, and some indirect evidence for a familial incidence has been noted by STEWART et al.[5] But if there were any kind of ordinary genetic transmission, convincing pedigrees would by now have been reported in substantial numbers. Possibly a few cases, especially those with associated disorders, are familial; but this does not affect the conclusion that the majority of cases must be sporadic—just as the familial incidence of colonic cancer associated with polyposis, or of œsophageal cancer associated with tylosis, does not affect the general conclusion that the majority of cancers at these sites are essentially non-genetic. Whatever produces the condition probably acts between fertilisation and the time of differentiation of the gonads: it may concern the mechanism of fertilisation or the development of either of the individual gametes that take part in fertilisation, but it seems most unlikely to be any more remote than this. MOORE's suggestion that hormonal balance at the crucial pregonadal stage of fœtal development is at fault is as good a hypothesis as any—indeed, something similar was once put forward in these columns [14]—but it rests on no solid evidence.

Dr. FERGUSON-SMITH's paper, besides consolidating the evidence for a high incidence in mental defectives, describes a unique series of prepubertal cases. He has established that in the testes at this stage the only recognisable lesion, and very probably the essential lesion, is a conspicuously low content of germ-cells. This makes it worth while reconsidering a hypothesis advanced by WITSCHI.[15] WITSCHI showed that in amphibia the number of germ-cells reaching the gonad profoundly affected the development of the gonad. If none reached it, no formed gonad would develop; if a normal complement reached it, the gonad would develop normally into ovary or testis according to the genetic sex of the embryo; but if an intermediate number reached it, the gonad tended constantly towards the male type, even in genetic females. He explained both Turner's syndrome and Klinefelter's syndrome on this basis: in Turner's syndrome no germ-cells reach the gonad anlage, which thus does not develop at all (so secondary sex characters develop in the neutral feminoid type); in Klinefelter's syndrome the germ-cells are deficient in number, so a male gonad is produced even in genetic females. This is a considerable simplification of WITSCHI's hypothesis, but it probably represents the useful bones of it. FERGUSON-SMITH's argument that a similar deficiency of germ-cells is found in the testes in some other conditions (notably in undescended testes, where the observation is an important one) is not altogether relevant; for these are all genetic males, and it is the possible effect of germ-cell deficiency in genetic females which chiefly concerns us. WITSCHI produced his germ-cell deficiencies in amphibian larvæ by allowing ova to become over-ripe before fertilisation; one shudders at the difficulties

1. Moore, K., Barr, M. L. *Lancet*, 1955, ii, 67.
2. Plunkett, E. R., Barr, M. L. *ibid.* 1956, ii, 853. Bradbury, J. T., Bunge, R. G., Boccabella, R. A. *J. clin. Endocrin.* 1956, **16**, 689.
3. Segal, S. J., Nelson, W. O. *J. clin. Endocrin.* 1957, **17**, 676.
4. Grumbach, M. M., Blanc, W. A., Engle, E. T. *ibid.* p. 703.
5. Stewart, J. S. S., Ferguson-Smith, M.A., Lennox, B., Mack, W. S. *Lancet*, 1958, ii, 117.
6. Polani, P. E., Bishop, P. M. F., Lennox, B., Ferguson-Smith, M. A., Stewart, J. S. S., Prader, A. *Nature, Lond.* 1958, **182**, 1092.
7. Wiedemann, H-R., Romatowski, H., Tolksdorf, M. *Artzl. Wschr.* 1957, **12**, 857.
8. Grumbach, M. M., Barr, M. L. *Rec. Progr. Horm. Res.* 1959, **14**, 255.
9. Ferguson-Smith, M. A., Lennox, B., Mack, W. S., Stewart, J. S. S. *Lancet*, 1957, ii, 167.
10. Ferguson-Smith, M. A. *ibid.* 1958, i, 928.
11. Prader, A., Schneider, J., Zubtin, W., Frances, J. M., Ruedi, K. *Schweiz. med. Wschr.* 1958, **88**, 917; *Lancet*, 1958, i, 968.
12. Campbell, H. *Brit. med. J.* 1958, i, 429.
13. Davidson, H. A. *ibid.* 1949, ii, 1328.
14. *Lancet*, 1956, ii, 127.
15. Witschi, E., Nelson, W. O., Segal, S. J. *J. clin. Endocrin.* 1957, **17**, 737.

involved in any attempt to prove or disprove the influence of the age of the maternal ovum at fertilisation on the occurrence of Klinefelter's syndrome. It is in fact when one comes down to details a most unsatisfactory hypothesis in many ways; but it can certainly be credited with being more exactly in accordance with Dr. FERGUSON-SMITH's new findings than any other.

Dr. FERGUSON-SMITH's suggestion that the clumsy and now inaccurate name "Klinefelter's syndrome" be replaced by "microorchidism" will repel those who believe that there is already enough confusion of names in this field. Yet the suggested name is neater and hardly less precise than seminiferous-tubule dysgenesis (the current transatlantic favourite, with several inferior variants) or hyperplastic medullary gonadal dysgenesis.[16] Eponyms are still being coined for the testicular feminisation syndrome.[17] Perhaps opinions in this field are still too fluid for successful attempts to codify nomenclature; but confusion will grow if some agreement is not reached soon.

Treatment of Cleft Lip and Palate

IN the past decade the surgical repair of clefts involving lip and palate has been increasingly in the hands of plastic and pædiatric surgeons, and accordingly the number of operations by each surgeon has grown: REIDY,[18] for instance, reviews 370 personal cases. Experience on this scale has already helped to clarify ideas; and surgical methods, though far from standardised, are tending to become uniform. About 800 children are born each year in Great Britain with clefts of lip or palate (about half are of the severe "complete" type); and there is, alas, no likelihood of any substantial reduction in this incidence. Happily results of treatment are in general improving.

Ten years ago LE MESURIER,[19] of Toronto, described his remarkable quadrilateral flap operation for repair of the primary lip defect. Possibly the only valid objections to this method are that the well-tried operation of VEAU [20] is simpler for the young surgeon to learn and tends to conserve tissue more certainly. The best age for primary operation on the lip is generally believed to be about three months; but in recent years STRAITH and his colleagues [21] in Detroit have reported success from operating in the first week of life, using local anæsthesia.

Repair of the palate is at once more dangerous and less urgent than repair of the lip. The main object is to create the conditions necessary for perfect speech, and operations on infants under the age of a year are neither profitable nor safe. On the other hand there is increasing evidence that if repair is deferred until the child is three or more years of age, good speech will be obtained only after intensive speech therapy; but a few orthodontists prefer late surgery. Orthodontic supervision from an early stage is essential; for the alveolar deformity, unless controlled by the orthodontist, may be accentuated by lip repair, and perpetuated by palatal repair. With good will, imagination, and experience a co-ordinated plan can be arranged. Experienced surgeons differ on the technique for repairing the palate; but there are few techniques that do not show the influence of VEAU's classic work [22] (developed by WARDILL and clarified by KILNER), with its emphasis on extensive anatomical mobilisation and on strict preservation of physiological function. Through VEAU's teaching we have learned that repair of the palate should comprise not a static but a dynamic reconstruction.

In 1931 VEAU reported a 10% operative mortality following repair of palates in babies aged a year or less. More recent figures, though on the whole better, are still in some instances discouraging. FRASER and MCCREDIE,[23] discussing planned operations of this kind, say plainly that "the death rate should be nil"; and in their own series the mortality was reduced from 4·9% to 0%. By contrast other recent reports show an operative mortality varying from 2% to 5·5%. A common cause of the "illness of trauma", and of death, is insidious and perhaps unrecognised loss of blood: for a child of three months a blood-loss of 4 oz. corresponds, on the basis of weight ratio, to a loss of about 3 pints in an adult. TEMPEST [24] reports an average blood-loss of 17% of the normal blood-volume in young children undergoing repair of palate. Close attention to hæmostasis throughout each phase of the operation is essential, and many surgeons find limited infiltration with saline-adrenaline solution helpful. DAVIES and DANKS,[25] reviewing 500 consecutive lip and palate operations, enumerated preoperative criteria of fitness for surgery and for general anæsthesia. They suggested that the infant should weigh at least 10 lb. and that the hæmoglobin level should be "normal" for age. (Healthy children in their first year are not expected to have a hæmoglobin level that would be "normal" for an adult, but many babies awaiting lip operations have a level as low as 60%. Few of these require blood-transfusion; and the main elements in therapy are patience, proper feeding, and administration of iron—intramuscularly in stubborn cases.) In addition the infant should be not only free from infection but evidently in good health—and here the report of an experienced ward sister is invaluable. DAVIES and DANKS and their colleagues applied these criteria in 500 cases, mostly under the age of 2, operating with general anæsthesia; 1 child died. These results were obtained in a unit where, at different periods, at least a dozen surgeons, including several registrars under training, were concerned.

The management of the exceptionally prominent premaxilla in some cases of bilateral cleft has excited controversy. Sometimes there is severe bony deformity with an anterior displacement of 20–25 mm. Some surgeons, influenced by "orthopædic principles",

16. Stewart, J. S. S. *Lancet*, 1958, i, 161.
17. Vaish, R., *Brit. med. J.* 1958, ii, 1386.
18. Reidy, J. P. *Ann. R. Coll. Surg. Engl.* 1958, **23**, 341.
19. Le Mesurier, A. B. *Plast. reconstr. Surg.* 1949, **4**, 1.
20. Veau, V. Bec-de-lièvre. Paris, 1938.
21. Straith, R. E., Teasley, J. L., Moore, L. T. *Plast. reconstr. Surg.* 1955, **16**, 125.
22. Veau, V. Division Palatine. Paris, 1931.
23. Fraser, I., McCredie, J. A. *Brit. med. J.* 1955, ii, 867.
24. Tempest, M. N. *Brit. J. plast. Surg.* 1958, **11**, 34.
25. Davies, R. M., Danks, S. *Anæsthesia*, 1953, **8**, 275.

believe that the position of the premaxilla after surgical replacement should be maintained by mechanical fixation with pins or plates. But even in expert hands such elaborate measures may cause trauma, with ischæmic atrophy of the vital alveolar keystone. For these difficult cases BATTLE [26] has suggested a safer approach. First the lip on one side is repaired, in order to ensure an adequate blood-supply to the adjacent bone. With this established, prevomerine bone can safely be resected a few weeks later when (at the same operation) the lip repair is completed. The reconstituted oral sphincter proves an admirable agent for retaining the replaced premaxilla.

Promising results are also being derived from other approaches—for instance, stimulation in the neonatal period of growth of palatal and alveolar bone by intra-oral appliances; special radiographic and cineradiographic techniques; pharyngoplasty (using either a central mucosal flap, or the lateral muscle flaps introduced by HYNES [27]); and plastic procedures to the nasal bones, septum, nostrils, and lip to correct during adolescence external deformities, which are often severe.

Annotations

CANCER CELLS IN THE BLOOD

DETECTING cancer cells in the blood is not as formidable a task as looking for a needle in a haystack. An excellent detailed study was published by Engell,[28] of Stockholm, in 1955. He set out to reproduce the work of Pool and Dunlop [29] in 1934. They had found abnormal cells in the blood of 17 out of 40 patients with advanced malignant tumours, using the simple method of hæmolysing the red cells with acetic acid and embedding and sectioning the remaining cellular elements. Engell hæmolysed with saponin, using only 2–5 ml. of blood, and sectioned the deposit. Moore et al.[30 31] separated the red cells by sedimentation with fibrinogen, and prepared smears from the buffy coat obtained by centrifuging the supernatant plasma. In order to free the tumour cells from some of the leucocytes Roberts et al.,[32] having sedimented the red cells with fibrinogen, centrifuged the plasma over an albumin solution of specific gravity 1065. Most of the leucocytes, being heavier than the tumour cells, passed through the albumin layer, leaving the tumour cells at the plasma-albumin interface. Smears were made of this layer, as well as of the heavier layer below the albumin, in case some tumour cells had been carried into it. Even so, the method was not quantitative. Engell estimated that the loss of tumour cells by his own method was 15–20%. To reduce this cell loss and destruction, Malmgren et al.[33] employed streptolysin-O to get rid of the red cells and polymorph leucocytes, and filtered the entire preparation through small-pore filters, as described by Seal [33] for concentrating cancer cells in large quantities of fluid. The results in 100 patients have now been published.[35]

That cells shed from tumours can be recovered from peripheral blood, or from blood draining the cancer site, is now well established; and the proportion of positive results found in a particular series is not by itself informative. Engell related the finding of cells to the histological class of the tumour in patients with carcinoma of the rectum and colon. Broders grade-II tumours gave only 35% positive, grade III 78%, and grade IV 100%. On the other hand there appeared to be no relation to the local spread of the tumour. Tumour cells were found at operation in the venous blood draining the site with almost equal frequency in patients who developed metastases or recurrence and in those who did not; but the evidence from this series is certainly not sufficient to conclude that cells in the venous blood have no prognostic significance at all in surgically treated patients. Laboratory animals may need to have very large numbers of cells injected intravenously to produce metastases in the lungs[31]; and possibly clumping of cells and the size of the clumps are more important than the total numbers of cells escaping from primary tumours. Engell found no significant difference in the number of cells recovered from the venous blood before and after manipulation of the tumour. Roberts et al., on the other hand, had 5 patients with positive results only after manipulation, and concluded from this and other evidence that surgical manipulation did lead to dissemination of tumour cells.

If cytotoxic agents can prevent or delay such free tumour cells or clumps forming tumour "colonies", their administration to patients before, during, and after surgical resection would be rational. Nitrogen mustard [36] and triethylene thiophosphoramide [37] have been reported to have this effect in rats; and Cole et al. [38 39] have been using nitrogen mustard as an adjuvant to the resection of cancers, giving not more than 0·1 mg. per kg. body-weight in each individual dose and 30 mg. for the total course of treatment. The fate of these patients is being compared with a concurrent control series; postoperative complications have been greater in the treated patients. A large study along similar lines has been organised by the National Cancer Institute of the U.S.A. This experiment in large-scale cooperation in the treatment of cancer should give interesting information, even though the results may not hold immediate promise of improvements in therapy.

ARTHROPOD-BORNE VIRUSES

FOR many years the Rockefeller Foundation's virus research programme has been concentrated on the arthropod-borne (or arbor) viruses, and this subject is reviewed in the Foundation's report for 1957.[40] The programme has involved world-wide study of the type, distribution, and incidence of viruses transmitted by the bite of arthropods, and of the infections that these viruses produce in man and domestic animals throughout the world. The problem is a large one which tends to increase as investigation throws up more facts. It is being tackled

26. Battle, R. J. V. *Brit. J. plast. Surg.* 1954, **7**, 217.
27. Hynes, W. *ibid.* p. 242.
28. Engell, H. C. *Acta chirg. scand.* 1955, suppl. 201.
29. Pool, E. H., Dunlop, G. R. *Amer. J. Cancer*, 1934, **21**, 99.
30. Sandberg, A. A., Moore, G. E. *J. nat. Cancer Inst., Wash.* 1957, **19**, 1.
31. Moore, G. E., Sandberg, A. A., Schuberg, J. R. *Ann. Surg.* 1957, **146**, 580.
32. Roberts, S., Watne, A., McGrath, R., McGrew, E., Cole, W. H. *Arch. Surg.* 1958, **76**, 334.
33. Malmgren, R. A., Pruitt, J. C., Del Vecchio, P. R., Potter, V. F. *J. nat. Cancer Inst., Wash.* 1958, **20**, 1203.
34. Seal, S. H. *Cancer*, 1956, **9**, 866.
35. Pruitt, J. C., Hilberg, A. W., Kaiser, R. F. *New Engl. J. Med.* 1958, **259**, 1161.
36. Cruz, E. P., McDonald, G. O., Cole, W. H. *Surgery*, 1956, **40**, 291.
37. McDonald, G. O., Livingston, C., Boyles, C. F., Cole, W. H. *Ann. Surg.* 1957, **145**, 5.
38. Morales, F., Bell, M., McDonald, G. O., Cole, W. H. *ibid.* 1957, **146**, 588.
39. Cole, W. H. *ibid.* p. 594.
40. The President's Review from the Rockfeller Foundation Annual Report 1957; p. 29.

by the Foundation's virus laboratories in New York, working in association with field stations in South America, Africa, and India. It is a measure of the success of this work that any present discussion of arthropod-borne viruses is soon concerned with the researches of this group.

In the course of this programme more than 70 distinct viruses have been discovered. Their final identification rests entirely on immunological principles and has had to be largely carried out in the New York laboratories. Three immunological methods are used: hæmagglutination-inhibition, complement-fixation, and the more specific virus-neutralisation; and these have disclosed antigenic specificities along with a greater or lesser degree of immunological overlap among groups of these viruses. Many of the 70 viruses belong to three distinct families which have been called groups A, B, and C; within each group immunological and other biological characters are to some extent shared. Group A includes the viruses causing the eastern, western, and Venezuelan forms of encephalitis in the Americas; and one new member from South Africa and two from Malaya have recently been added. Group B is the largest one and is responsible for many of the arthropod-borne infections that are most important to man. Within group B several subgroups can be recognised. One consists of yellow-fever and closely related African viruses. A second subgroup consists of the two immunologically distinct types of dengue virus. A third contains encephalitis viruses such as St. Louis, Japanese B, and Murray Valley. A fourth subgroup is called the Russian tick-borne complex, although the first member of this group was actually discovered in Scotland in 1930, where it is the cause of a severe disease of sheep—louping-ill. This virus was found to be immunologically almost identical with the Russian spring-summer encephalitis virus isolated in 1937 from cases of encephalitis in man in Siberia. Closely related viruses have been shown by Soviet workers to be responsible for Omsk hæmorrhagic fever and biundulant fever, and have also been isolated in several countries of eastern and central Europe. In all cases these viruses, unlike most other arthropod-borne viruses, were transmitted by the bite of ticks, and the same is true of two new members of the group isolated in Malaya and India. Group-C viruses have so far been isolated only in South America, where serological evidence suggests that infection of man is very prevalent although the clinical manifestations are little known. Serological surveys also suggest that these viruses may be prevalent in Africa too. Groups A, B, and C account for about half the arbor viruses, while the other half consist of a heterogeneous collection which includes viruses causing epizootics in domestic animals as well as sandfly-fever of man.

The clinical manifestations of infection with the arthropod-borne viruses are extremely varied and provide no help in distinguishing the different viruses. Yellow fever itself can vary greatly in severity. Within the Russian tick-borne complex the new Indian member (Kyasanur forest disease virus) apparently produces a picture not unlike yellow fever with a fairly high mortality. Omsk hæmorrhagic fever is rarely fatal; it is associated with severe hæmorrhage but no manifest disorder of the central nervous system. On the other hand, in Russian spring-summer encephalitis nervous involvement is often severe, as in louping-ill in sheep. Finally biundulant fever rarely causes fatal infections and shows two febrile periods, often separated by an afebrile interval of a few days.

This type of research makes demands on epidemiologists, virologists, entomologists, and many others. How is it done? The Foundation's report tells the story of the events surrounding the isolation in India of a virus belonging to the Russian tick-borne complex. First news was that monkeys in Kyasanur forest, Mysore State, were dying in large numbers, and an expedition from the Foundation's field station in Poona discovered in human beings fatal cases which were clearly associated with their entry into the forest. Strains of virus isolated from dead monkeys and from cases in man proved to be closely related to Russian spring-summer encephalitis virus, and this at once suggested that the disease might be spread by ticks. Mosquitoes were in fact very few in this region, and the virus was soon isolated from ticks found in the area. Methods of controlling or eradicating ticks were then considered by the Indian Government, while the Walter Reed Army Institute of Research in Washington offered to make 50,000 doses of vaccine. Unfortunately the Indian strain of virus showed poor antigenic potency; so it was decided to make vaccine from the closely related Russian spring-summer encephalitis virus instead, and vaccination is now being carried out with the help of a $100,000 grant from the Rockefeller Foundation. This vaccine should give protection, but two disadvantages anticipated are that three injections will be required and that immunity may not last very long. A living attenuated vaccine, along the lines of the 17D strain of yellow-fever virus, is therefore being sought.

An interesting by-product of the Foundation's investigations arose from the fact that only in Africa have viruses closely related to yellow-fever virus been found. Yellow fever is known to be present in tropical America, but no closely related viruses have been found there. This supports strongly the belief that Africa was the original home of yellow fever. Since yellow fever can be maintained in a cycle involving only man and mosquitoes, it could well have been introduced into America in the era of sailing ships. The greater severity of yellow fever in America than in Africa also favours the supposition that it has not been long established in America.

The arthropod-borne viruses characteristically show great immunological variability in space—different viruses are apparently largely confined to a given area, maintaining over long periods their behaviour in that area. The influenza viruses, on the other hand, show great variation with time. New immunological variants of influenza virus, such as the recent Asian viruses, soon become widespread, virtually replacing previous varieties throughout the world. The enteroviruses, including viruses such as poliomyelitis and Coxsackie and the large variety of viruses now being isolated from human fæces, appear to be widely seeded throughout the world. It is an interesting exercise in ecology to try to relate these differences in distribution to the different routes of transmission of these three groups of viruses. But they all pose practical problems in the laboratory. The widespread use of tissue-culture techniques for isolating viruses in the past ten years has already yielded large collections of unclassified viruses in search of a disease, and there will surely be many more to come. Most of these new viruses may prove to be harmless commensals, but some may have great epidemiological importance. There is no escape, therefore, from

the need to identify these new viruses, and collaboration at an international level will be needed to prevent a great deal of wasteful investigation. Another need is for easier methods of virus investigation which would reduce and simplify necessary comparisons with known viruses. In all these directions the Rockefeller Foundation has given a lead which others should surely follow.

THE UNDESCENDED TESTIS

COMMENTING on a leading article [1] several correspondents implied that discussion on the management of the undescended testis is doomed to futility until we know more of its natural history. We are at last distinguishing maldescent from incomplete descent, and most of us are trying to distinguish between the retracted and the incompletely descended organ; but Dr. Winkel Smith [2] rightly pointed out that " no material yet exists which can conclusively indicate the right approach to this very important clinical subject ". A survey of schoolboys conducted by the East Anglian Branch of the Society of Medical Officers of Health [3] must be acclaimed as a serious effort to collect such material. About forty school medical officers carried out the investigation in the areas of six local authorities between September, 1956, and July, 1957. The facts were collected at the routine medical inspection of schoolchildren aged 5, 11, 14, and in some areas 8 years. School-leavers are also examined; and the ages of these ranged from 14 to 17. Of 23,398 boys scheduled for inspection 22,218 were examined for unilateral or bilateral empty scrotum.

In his pertinent criticism of earlier figures, Mr. Scorer [4] suggested that it was wrong to imply that " there is a natural process of descent over a period of many years "; and that our rough estimate of the prevalence of non-descent (in 10% at birth, in 2% at puberty, and in 0·2% of men) rested on questionable evidence. Instead of relying on earlier statistics, collected without preliminary definition of the retractile testis, he had himself examined 1500 full-term infants (weighing 5 lb. 9 oz. or more) at birth and had found one or both testes undescended in 51 (3·4%). By the end of the first month of life the testes had descended in about half of these; and by the end of the first year the prevalence of non-descent in the first 1000 was 0·7% [5]. His findings led him to conclude (and his conclusions are shared by many) that " spontaneous descent takes place early in life but very seldom later ", and that " the incidence of undescended testis remains almost constant from infancy onwards " [4]. In the East Anglian survey, on the other hand, unilateral undescended testis was found in 4·3% of 5-year-old boys, in 4·5% of 8-year-olds, in 3·5% of 11-year-olds, and in only 0·6% of school-leavers. The prevalence of bilateral empty scrotum was 2·0% at 5 years, 2·3% at 8 years, 1·8% at 11 years, and 0·1% at school-leaving age. The East Anglian workers themselves have subjected these figures to searching criticism, which illustrates the many pitfalls of collective surveys.

In one of the six local-authority areas the school health service is divided, for administrative purposes, into nine districts; and since " there is no great overlap between the duties of school doctors in adjoining [districts], it was thought that variations in the results for the different [districts] might give an estimate of the effect of different observers ". These differences proved considerable. The prevalence of unilateral empty scrotum at 5 years varied from 0·71% recorded in one district by one observer to 14·65% recorded in another district by another observer; and the corresponding ranges in 8-year-olds and 11-year-olds were 1·06–10·41% and 2·30–5·59%. The pooled results showed less variation; but this was still wide. (Unilateral empty scrotum was found in 1·8% of 1600 5-year-old boys in one area and in 5% of 2000 boys in another.) Nor is the suggestion that " the lowest estimates are likely to be the most accurate " entirely acceptable. It is true that by far the most important source of error is retraction; but it is not impossible to " miss " an empty scrotum—mistaking a hernial sac with omentum, fluid, or bowel for a testis.

It might be supposed that, even if the figures are too high, the trend between the age of 5 years and school-leaving strongly suggests that a considerable proportion of undescended organs descend just before or during puberty. But this would not be a fair conclusion, since at puberty many retractile testes lose their retractility. Retraction remains, in fact, the bugbear of all statistical work on this important subject; and this is the more depressing since we are still almost totally ignorant of its causes and mechanism.

1. *Lancet*, 1957, ii, 989.
2. Winkel Smith, C. C. *ibid.* 1957, ii, 1172.
3. Report of the East Anglian Branch, Society of Medical Officers of Health. *Med. Offr*, 1958, **100**, 379.
4. Scorer, C. G. *Lancet*, 1957, ii, 1124.
5. Scorer, C. G. *Arch. Dis. Childh.* 1956, **31**, 198.

THE LEAKING UMBRELLA

IT might be regarded as misfortune that Sanchez-Ubeda and his colleagues [1] undertook to investigate the value of what is vulgarly known as the antibiotic umbrella, just as the staphylococcus was raising its ugly head; but there is a moral to the story. They originally intended to observe a considerable series of postoperative cases, since " clean " cases were expected to yield a low prevalence of infection—thus requiring a large series to reveal statistical significance. In fact their study ceased after 511 consecutive cases had been seen, because the staphylococcus had mocked them. Alternate cases (255 in all) were given antibiotic " cover " and were compared with the control group of 256 in which no antibiotic was given. In 152 cases the procedures (such as alimentary resection) might be expected to give rise to contamination; only 359 were frankly clean cases. In these the complication-rate in terms of both wound and respiratory infection was quite unaffected by the administration of antibiotics, the wound-infection rate being 5% in both treated and control groups; but allergic manifestations put the antibiotic group at a disadvantage, raising the overall complication-rate to 9·5% compared with 5·6%. In the 152 " dirty " cases the incidence of wound infection was identical in the two groups, being just over 14%; the total complication-rate was also equal at 22–23%. These results reflect those of McKittrick and Wheelock in a pilot study undertaken in the era before the resistant staphylococcus.[2]

In the investigation by Sandrez-Ubeda et al. the antibiotics administered were penicillin and streptomycin, which would have no effect on resistant staphylococci. The moral is that prophylactic blunderbuss therapy with no specific organism in mind is like shadow-boxing with an elusive unidentified opponent; and it is as pointless as the blind administration of antibiotics when vague and uncertain disorder is present. Dietrick et al.[3] point out how abdominal symptoms may thus become masked so that conditions such as acute appendicitis remain undiagnosed and yet unrelieved, leading at best to lengthy illness, at worst to catastrophe.

1. Sanchez-Ubeda, R., Fernand, E., Rousselot, L. M. *New Engl. J. Med.* 1958, **259**, 1045.
2. McKittrick, L. S., Wheelock, F. C. *Surg. Gynec. Obstet.* 1954, **99**, 376.
3. Dietrick, R. B., Byrd, C. W., Lawson, J. A. *Ann. Surg.* 1958, **148**, 985.

Conferences

EVALUATION OF DRUGS

A SYMPOSIUM on Progress in the Evaluation of Drugs was held in London on Jan. 22 by the Association of Medical Advisers in the Pharmaceutical Industry.

The meeting was opened by Dr. T. B. BINNS, who said that the prestige of British therapeutics had been raised by the specially designed clinical trials conducted by teams attached to the M.R.C., and by statisticians such as Prof. Bradford Hill. New drugs were now being produced by the chemists at a rate quicker than that at which they could be tested by the pharmacologists and clinicians. Yet proper evaluation was essential to prevent worthless drugs from being released. The effective testing of new drugs was a laborious process.

Summaries of the four opening papers and brief accounts of the discussions appear below.

Preliminary Trials of New Drugs in Man

Prof. C. A. KEELE

New drugs are mostly discovered by laboratory research, which demonstrates pharmacological actions in animals and suggests therapeutic applications in man. Acute and chronic toxicity tests are performed to estimate the probable safety of new drugs in human beings. However, species differences in responses make an accurate forecast difficult. A preliminary trial in man is a crucial stage in the development of any new drug. There are two phases:

1. *Tests on volunteers* are designed mainly to find the suitable dose to administer to patients. The dose is calculated from animal experiments and is based on body-weight or surface-area. It is best to begin with a small fraction of the calculated dose and work up to a dose which produces some side-effects. These initial tests are really a part of the pharmacological study of the drug, but give little information about its therapeutic value. A drug may be discarded because of toxic effects at this stage.

2. *Tests on patients* are designed to study actions and therapeutic effects, to determine whether the drug should be submitted to a controlled clinical trial, and to decide whether to pursue further work on the group of compounds to which the new drug belongs. The administration of new drugs to patients involves important ethical considerations. The patient's consent and cooperation should be obtained whenever feasible. The doctor in charge of the investigation should have received the drug himself in doses sufficient to produce side-effects.

I will illustrate these points by reference to some work which Dr. P. Flintan and I did at the Middlesex Hospital (1954). Adamson and Green (1950) had observed that some dithienylbutenylamine compounds were powerful analgesics in animals. We noted in normal persons that the drugs acted generally like morphine and pethidine in relief of pain and in depressing respiration, but had a greater hypnotic effect and less liability to produce nausea and vomiting than morphine. Two of the compounds produced a marked muscular weakness in a few normal subjects.

Two of the drugs were administered to patients, chiefly with postoperative pain. The better analgesic unfortunately produced muscular weakness and was rejected. The remaining drug, compound 1C50, was studied in 200 patients in a "single blind" trial in which the observer (P. F.) but not the patients knew the nature of the injected drug. We were not justified in giving to patients a drug of questionable safety as an unknown. The conclusions were:

1. Compound 1C50 was an effective analgesic, slightly more potent than pethidine and weaker than morphine.

2. It was not recommended for a controlled trial because: (*a*) 1C50 was not therapeutically superior to morphine; (*b*) 1C50 was unstable in solution; (*c*) in a few patients the drug produced a purple urine, apparently harmless, due either to indigo compounds or to drug metabolites.

Many new drugs are rejected after preliminary trial in patients because of lack of expected therapeutic effect or undue toxicity. Important practical decisions have to be made on the basis of accurate, but not fully controlled, observations. A controlled clinical trial is not justified, and cannot be satisfactorily conducted, until an adequate preliminary trial has been performed.

There is an element of risk attached to every preliminary trial of a new type of chemical compound. It is not an activity for those who share the caution recommended by Alexander Pope to his critic: "Be not first by whom the new are tried, nor yet the last to lay the old aside". Advances come rather from those who feel that "faint heart never won fair lady! nothing venture, nothing win". However, one must remember that if the venture fails it is the patient who suffers most.

On Asking the Right Question

Dr. JOHN KNOWELDEN

The controlled field trial properly conducted is the most precise tool we have for measuring the effectiveness of therapy or prophylaxis. It is limited in its activity since it is simply an experiment set up to reject or confirm a hypothesis. Its scientific value must depend, therefore, on the choice of the right hypothesis to test. If the successes gained by this method in recent years are to be continued, careful planning will be required to ensure that trials are conducted to answer the right questions.

Four questions might be asked before the final plans for a trial are drawn up:

1. *What disease?*—If there is heterogeneity in the illnesses suffered by the patients admitted to a trial, the response of one specific group may be masked by the insensitiveness of the remainder. In general it is best to choose the illness most likely to respond to the new therapy; it may be necessary to define not only the clinical picture but also the ætiological type, stage, and severity of disease to be included, and to provide rigid diagnostic criteria for this purpose. On other occasions, however, it may be useful to test the overall value of a new treatment in a well-recognised syndrome of mixed ætiology, and the diagnostic criteria would then be correspondingly less strict.

2. *What treatment?*—Controlled trials have sometimes been initiated when too little has been known of the dose-response curve or toxicity of the drugs to be tested; and the choice of dosage, mode, or period of administration have been largely guesswork. Assuming good pharmacological data, a trial may be set up to answer one or other of the questions: (*a*) is the new treatment better than nothing at all; or (*b*) is the new treatment better than established methods? The regime offered to patients in the control group will be decided by whichever question is appropriate.

3. *What patient?*—The type of patient to be admitted to the trial may depend on whether it is intended to test therapy on those most likely to respond, or on those in whom benefit is most urgently required. Age, sex, and environmental and social factors may have to be considered in defining the persons to be admitted.

4. *What indices of measurement?*—Progress under treatment may be measured objectively or subjectively, by clinical or

laboratory tests. The methods may be chosen to measure survival, cure, palliation, or rehabilitation. They need precise definition and may themselves require testing to ensure that they are reproducible and appropriate to the illness. The problem of weighting different indices applied to the same patients, when these respond differently, may arise and should be anticipated.

To answer these four questions will require detailed knowledge of the natural history and pathology of the illness and the pharmacology of the drug; and, to provide this, pilot trials may be necessary. Only after such preparation can controlled trials realise their full potential.

Discussion

Dr. P. ARMITAGE referred to the use of sequential analysis in clinical trials. This was a technique in which observations were analysed continuously as they became available. The trial could be stopped at an opportune moment—for example, when it became obvious that there was a difference between two treatments. Sequential analysis saved time and prevented bad treatment being given—which might well happen in the usual randomised double-blind clinical trial. In sequential analysis the length of the trial was not predetermined, although the maximum length might be. Analgesics, hypnotics, cough suppressants, bronchodilators, tranquillisers, and corticosteroids could be examined by this method. The technique was also suitable for evaluating the treatment of chronic disease, when the response could be observed only by lengthy follow-up.

In pilot trials sequential analysis was relevant. The pilot trial was in fact the beginning, and it could be stopped at any convenient point; if the treatment appeared promising, the trial could continue. In a clinical trial of a new drug, the effect of increasing doses should be noted and a dose-response curve constructed. Another important aspect of drug-testing was the evaluation of side-effects. Many thousands of drugs were tested every year on both sides of the Atlantic, yet only a few reached the medical profession. As more were synthesised than could be tested, screening tests should be improved to whittle down the number going for clinical trial.

Clinical judgment was needed in trials with new drugs. The investigator's previous experience enabled him to tell to what extent the patient was responding to treatment. In some trials—for example, with analgesics—the information obtained was entirely subjective.

Dr. MARY LOCKETT said that preclinical tests on volunteers were important. They gave the clinician an idea of the dose before the drug was given to the patient; they often revealed its side-effects and dangers; and they afforded an opportunity to study its distribution and metabolism. Metabolites, which might produce undesirable actions, could be studied. In the case of some drugs the dose required to give therapeutic blood levels could be found before they were ever given to a patient. The plasma level at which toxic side-effects were produced might also be found. Much of this work could not be done on animals. Dr. Lockett thought that, generally speaking, medical and science students were bad subjects for such preclinical trials as they were often introspective and expected something to happen. It was sometimes possible to dispense with a placebo when using volunteers, and to compare the effects of two drugs directly.

Prof. G. M. WILSON (Sheffield) referred to the natural history of the disease under investigation. Spontaneous improvement could occur in many conditions, and this should be considered in evaluating the effect of new drugs. Some trials with new drugs were relatively easy—for instance, those used in the treatment of diabetes and pernicious anæmia, where laboratory control was possible. Others, involving, for example, the evaluation of hypnotics and analgesics, were notoriously difficult, particularly in busy teaching hospitals. These drugs were better examined in general practice than in hospital. The placebo played an important part in the evaluation of drugs producing subjective effects. One method of testing was to give patients the drug under test and a placebo, and to ask them which they preferred. Sometimes a second drug could be included in the trial, but generally speaking the best results were obtained when the patient had to choose one of two preparations. While he valued the work done by M.R.C. teams in highly specialised trials, Professor Wilson said that it was not necessary to invoke their aid for all clinical trials. Quite useful work could be done in the smaller hospitals and by general practitioners. In the past many useless remedies had been employed because they had not been subjected to controlled clinical trial, or because they had not been tested outside the laboratory. He remembered as a student seeing a sodium-sulphate drip used for the treatment of anuria—a perfectly useless procedure based on incorrectly interpreted animal work.

Dr. E. T. KNUDSEN thought that it was unethical to give a patient a new drug before it had been evaluated in volunteers. It should be given to them in increasing doses until it produced side-effects, in order to find the maximum tolerated dose.

Dr. W. KENNEDY said that it was often not realised that there was an enormous individual variation in the response to the same dose of a drug.

Dr. F. WOLFF pointed out that it was useless to apply statistics to faulty data, particularly when the data were subjective and the observer error was great.

Dr. H. C. STEWART thought that some drugs might have a euphoriant action, and that it was necessary to exclude this before assuming that they had any specific action.

Assessment of Treatment of Mental Disorders

Dr. MICHAEL SHEPHERD

MOST of the drugs employed in the management of mental disorders are empirical remedies. They are difficult to evaluate, partly for the same reasons which apply to the treatment of much chronic non-lethal disease. Many of the major diagnostic groupings in psychiatry are heterogeneous and the factors of ætiological and prognostic importance are often poorly understood; in consequence, the untreated course of the individual condition may be hard to predict. In addition, the assessment of treatment is hampered by the paucity of reliable indices of response since the somatic accompaniments of mental disorder tend to be inconstant and the psychological changes have not yet been clearly defined. The behaviour of psychiatric inpatients has been widely used in the study of response to treatment, but it is difficult to measure and is influenced by numerous non-specific factors. Similarly, the inferences drawn from large-scale statistics relating to mental-hospital populations must be made with great caution. Evaluation of the treatment of patients outside hospital suffering from minor psychiatric disorders in-

volves subjective assessments made by either the observer or the patient; safeguards against bias are essential.

The many comparative group trials which have been conducted in the field have yielded information of limited value so far, principally because of the difficulties of constructing representative populations and the indefinite nature of the criteria of response. Ethical principles must be observed with particular care in the treatment of clinical mental disease. In our present state of knowledge the data obtained through drug trials could be supplemented by attempts to study more intensively: (*a*) the biological basis of favourable therapeutic response when this occurs; (*b*) the development of the self-controlled trial for the study of low-grade psychiatric morbidity; (*c*) the building up of information about the movement of psychiatric populations in hospital which could be used for epidemiological inquiries. Much more research is needed in all these areas.

Tribulations and Trials

Dr. R. H. GOSLING

THE mere application of the accepted methods for the conduct of a clinical trial will not govern all sources of error.

The dose of the drug to be evaluated must be very carefully chosen, otherwise incorrect conclusions may be drawn; and therefore the use of more than one dosage level is advisable. A greater amount of preliminary work on normal volunteers might help in determining correct dosage; but it should be remembered that volunteers may not be truly representative of the general population, and that certain states of mind can influence the act of volunteering. Subjective information so obtained should consequently be accepted with some caution.

A clinical trial on any section of the community which is not representative of the general population may give misleading results.

If untreated controls are not included in a trial and laboratory criteria are used to support clinical appraisal, the investigators should be aware that these criteria may be derived from observations coloured by the intervention of the human element. Other apparently objective criteria, such as measurement of the blood-pressure, can be influenced by the investigator's impressions of the patient's current treatment. A natural decline in the mortality of a disease may be attributed to the introduction of a new drug if there are no untreated controls in the study.

The double-blind control is essential in certain investigations, in order to deal with bias on the part of the investigator and expectation on the part of the patient; but its use does not guarantee the reliability of results obtained. The double-blind control does not prevent an erroneous conclusion being drawn if extraneous forces are present to such a degree that the sensitivity of a trial is considerably diminished. It does not alleviate the situation wherein the investigator is dependent on the obedience of the patients to instructions. They may fail to take the treatment prescribed; and the practice whereby outpatients are required to fill in a questionnaire after a period on a drug is often unsatisfactory, since recent events stand out more clearly in the memory. A leading questionnaire may actually suggest symptoms to the patient.

Outpatients who are suffering from a serious disease often do not comply with instructions, and when a clinical trial is carried out in a comparatively mild condition there is even less stimulus for the patient to adhere to directions.

Furthermore, it is impossible to apply the double-blind control to all clinical trials.

A spontaneous change in the course of a disease may be attributed to placebo reaction, and therefore a control period or control group where nothing of any sort is given may be necessary. When a drug is compared with a placebo, a side-effect may reveal the active drug to patient or observer.

It is generally desirable that the results of a clinical trial should be presented in a form which is of the greatest practical value to the practising doctor. Often, however, the most useful measurements, such as functional tests in rheumatoid arthritis, are very difficult to apply to a controlled trial involving considerable numbers of patients.

There are certain answers which a clinical trial cannot supply—toxic and other unexpected effects may arise only when the drug has been in general use for several years.

Discussion

Dr. W. R. S. DOLL referred to the variation between patients in response to therapy, and stressed the need for double-blind investigations. It was best for the patient to act as his own control; but in the treatment of certain conditions, such as peptic ulceration, this was impossible. The treatments to be compared should preferably be allocated to patients in a random manner, but this was not absolutely necessary. In the evaluation of a new drug the question asked was: "is it possible to make this patient better by the use of this drug?" Finding the answer might involve changing the dose of a drug according to the patient's needs during the trial. Dr. Doll did not agree that it was essential to lay down a strict dose schedule at the outset and to adhere to this implicitly throughout the investigation.

Dr. N. D. COMPSTON emphasised the great practical difficulties which faced a clinician undertaking a therapeutic trial. Owing to such difficulties it was often exceedingly difficult to adhere to the plan of experiment. Frequently there was a considerable fall-out of patients from a trial, and it was almost impossible to prevent this. In one recent trial with which he had been associated the duration of treatment was only a matter of days, yet of twenty-five patients eleven dropped out. In addition, the ward staff often failed to appreciate the need for clinical investigations, and it was important to obtain their full collaboration. When long follow-up was necessary it was difficult to retain the patients' cooperation.

As a result of what he had heard in the symposium, Dr. Compston now had great confidence that the substances offered to him for trial had undergone as extensive and as thorough preclinical testing as could be devised.

Dr. I. SUTHERLAND thought that many of the difficulties of clinical evaluation were due to the lack of precise definition of disease. The statistician was able to say whether there was a significant difference between two treatments but was not able to say how important that difference was clinically. However objective the criteria of success might seem, observer bias could not be entirely removed. Inert substances often produced short-term

improvement, but long-term improvement was rare. In clinical trials was it important to measure the effect, not only of drugs, but also of the environment and other factors which tended to produce recovery.

Dr. R. HODGKINSON (U.S.A.) thought that the methods of clinical evaluation used in Great Britain and in the U.S.A. were essentially the same. The pillars of clinical evaluation were careful planning, systematic observation and performance, and honest and courageous interpretation of the results. In America clinicians, even in small and isolated hospitals, were very research-conscious. Another difference was that there was no official body in Great Britain which corresponded to the Food and Drugs Administration. He thought that the clinician in charge of clinical trials should himself take the maximal dose which was to be used in volunteers in clinicopharmacological studies, and it was most important that the results of controlled clinical trials should be available before the decision to market a product was taken.

Dr. M. HAMILTON referred to the placebo response, which was of considerable importance in controlled investigations. Studies at Leeds had shown that there was no relationship between the patient's age, sex, or personality and his response to a placebo. The evidence did not support the concept of a placebo reactor and non-reactor.

Dr. A. A. BAKER emphasised the inherent difficulties of double-blind investigations. In his experience, rarely was it possible to conceal from the patient for more than a few days which was the active and which was the inert drug. Patients were generally able to distinguish easily the active drug by its subjective effects.

In his summing up Sir GEORGE PICKERING said it was praiseworthy that such a meeting should have been held under such auspices. The level of clinical and scientific integrity which had been achieved was high. It was most important in clinical evaluation that the right question should be posed and that the answer obtained should be to that question. For instance, because a substance lowered the blood-cholesterol level, it did not necessarily follow that this was of use in the treatment of atherosclerosis. He believed that one of the functions of a good physician was to produce in the patient a placebo effect. After all in his youth, not so long ago, that was the only criterion distinguishing a good from a bad physician.

HOSPITAL CROSS-INFECTION

IT is a sign of the times that a conference on the prevention of hospital cross-infection should have been convened by the regional board at Little Bromwich Hospital, Birmingham, on Jan. 16 under the chairmanship of Prof. JOHN SQUIRE. Significantly the conference was held in a hospital which until a few years ago was a fever hospital but which changed its character because of a dearth of patients; and ironically the delegates came to this erstwhile fever hospital from the fever hospitals of today—the general hospitals. The staphylococcus, though the principal villain paraded on the stage, was not without a supporting cast.

Description of Outbreaks

Dr. KEITH ROGERS (Birmingham) described epidemics in a children's hospital. These fell into three main groups: virus infections (in particular measles); infection with gram-negative bacilli; and infections with gram-positive cocci. He had found that the presence of one *Escherichia coli* carrier in a ward of patients with pneumonia would result in an infection-rate with this organism of 45%, thus extending the stay in hospital of each case from two weeks to thirty days or more; similar results were obtained from a series admitted for intussusception. After screening of every admission and separation of patients free from the organism from those excreting *Esch. coli*, enteritis had developed in only 9 of 137 cases of pneumonia. In his hospital, though infection spread readily on one floor, there was no spread vertically to other floors; this might be due to the movements of nursing staff, which were usually restricted to one level. In the summer months they had had to face a mystifying and serious outbreak of *Pseudomonas pyocyanea* infection, sometimes fatal, in patients with tracheobronchial fistula. The facts that in all the cases the patient had been operated on and the infection was not confined to one ward led the search for a source to the theatre, where ultimately a repository for a bronchoscopic sucker was found to be heavily contaminated. When this source was eliminated the epidemic ceased, but it recurred later owing to a concatenation of circumstances which brought about the return of the sucker and its sheath. Dr. Rogers had recently brought a staphylococcal epidemic under control after discovering that 6 out of 8 nurses with pimples and boils were carriers of phage-type 80.

Preventive Measures

Dr. W. A. Gillespie (Bristol) said that the colonisation with staphylococci of babies newly born in hospital should be delayed for as long as possible in order to prevent frank infection. With this in view he had attacked the blanket problem in nurseries and had arranged for chlorhexidine hand-cream to be used by the nurses. By using hexochlorophane as a dusting-powder he had prevented colonisation of the umbilicus, groin, and perineum but not the nose, for which he thought an ointment necessary. As a result of these measures the incidence of sepsis fell over two years to 0·8% from 7% in one nursery and from 9% in another for all babies retained during a ten-day period. He had seen no allergic sensitivity to hexochlorophane even when this was used in the bath-water. Other investigations he had undertaken concerned urological cases. After prostatectomy the incidence of urinary infection fell to 57% when closed drainage was used, to 23% when the operating cystoscopes were swabbed with chlorhexidine, and to 8% with preoperative urethral disinfection. 69% of cases of retention had urinary infection following open catheter drainage and 8% following closed drainage.

Infection in the Theatre

Dr. EDWARD LOWBURY (Birmingham) said that the incidence of infection in clean operation cases was rising: figures now reported were as high as 15–20%. The infection was usually staphylococcal, and only rarely tetanus or gas-gangrene. He found that 20% of surgical wounds were contaminated by the act of incision, and that 60% were infected by the end of the operation. Airborne contamination with staphylococci came from a source inside the theatre, with tetanus or *Clostridium welchii* from outside. The factors leading to contamination within the theatre were numerous. He recommended for the patient's skin 1–2% iodine in 70% alcohol, and for

the surgeon's hands hexochlorophane soap followed by a half-minute rinse in 70% alcohol and the possible use of neomycin-bacitracin glove powder to reduce contamination from the hands through holes in the gloves. Experimentally he had found that the bacterial count from hands covered with defective gloves but no powder was twenty times greater than when neomycin-bacitracin powder was used. Using slit samplers he had shown how air contamination builds up with movement within a badly ventilated theatre, whereas summation of each incident of increased air contamination does not take place when ventilation is corrected. By similar techniques he had correlated the concentration of air contamination due to poor ventilation with the infection-rate in a dressing-station for burns. In answer to a question, Dr. Lowbury stated that further work was needed on solutions for the sterilisation of sharp instruments since neither lysol, carbolic acid, the phenolics, nor chlorhexidine in alcohol could be guaranteed to destroy spores, though the addition of formaldehyde to a chlorhexidine-alcohol solution might suffice. Another speaker pointed out that there was no objection on metallurgical grounds to boiling or steam sterilisation of sharp instruments.

Blankets

Dr. ROBERT BLOWERS (Middlesbrough) described the sweep-plate technique for investigating blankets, the contamination of which (commonly with *Staphylococcus aureus*, *Ps. pyocyanea*, and *Esch. coli*) becomes worse after simple laundering. Proof through phage-typing had not been obtained of infection by one patient of the next to occupy the same bed, but blanket contamination undoubtedly spread infection less directly through intermediate agents such as a nurse's or doctor's hands or clothes. Woollen blankets might be rid of non-sporing organisms by immersion at 70°C; but agitation of the water damaged the blanket. Blankets could be sterilised by steam at 5 lb. pressure or by heating in an atmosphere of formaldehyde vapour—a laborious process. They could be made hygienically clean by washing and then disinfected with quaternary ammonium compounds—though this is not effective against gram-negative organisms. Though detached fibres of the blankets thus treated could then be seen to inhibit other organisms, the blankets on beds had no such effect, probably because of drying. After 20 such washes the blankets were too shrunken and hard for comfort; but the number of washes could be extended to 60 after the application of devices to minimise shrinkage. Until a feasible method of sterilising wool was found it was easier to turn to other materials. 'Terylene' was unsatisfactory since the "woolly" fibres become matted after repeated boiling: it also developed a high static charge with serious spark hazard. Probably the best material at present available was cotton in open or cellular wove; this was light and boilable, though susceptible to damage by tumbler-drying. Turkish-towelling, being cotton, was also boilable and hard-wearing; Calnan-mesh, a design based on string-mesh sandwiched between sheets of cotton-rayon mixture, was heavy, inflexible, and tedious to wash and dry. Dr. KEITH THOMPSON (Birmingham) had found that after 40 washes cotton blankets were still within 12–15% of the thermal efficiency of woollen ones. It was suggested that woollen blankets might be sterilised by subjection to radioactivity, but it seems that this caused disintegration after a few applications.

Carriers of Infection

Dr. ROBERT WILLIAMS (Colindale) declared that 50% of hospital staffs are nasal carriers of staphylococci and 20–25% of adults become so after 3 weeks in hospital. Besides the nose, the perineum was a potent source of contamination. Those most liable to colonisation by the staphylococcus on admission to hospital were those who were not nasal carriers before admission; carriers showed some immunity. Resistance to tetracycline rose to 100% after the drug had been administered for a week. The development of penicillin-resistant strains in a wound was due to cross-infection with resistant organisms, since it was unlikely that strains sensitive to penicillin could themselves become resistant—though erythromycin resistance did develop in this way. In answer to a question, Dr. BLOWERS emphasised that any member of the nursing or medical staff who developed a pimple or boil should be relieved of duties bringing him or her into contact with patients until the bacteriologist permits return to duty; and it should be borne in mind that the scar or crust at the site of a recent pimple still harboured many organisms.

The Pathologist's Role

Dr. KEITH THOMPSON (Birmingham) described the role of the hospital pathologist as that of hospital policeman who, by the exercise of intelligence and observation, could do much to mitigate infection through simple measures in outmoded buildings and with outdated apparatus in theatre, kitchen, and ward. Air currents could be deflected, cooking practices and the handling of food be kept to a high standard of hygiene, and ward sepsis reduced by such simple measures as the avoidance of overcrowding and the oiling of floors. Simple instruction in bacteriological principles to kitchen and other staff was obligatory and was appreciated by the staff. The responsibility lay with the doctor—primarily with the hospital pathologist.

Dr. W. H. BRADLEY (London) reiterated that the responsibilities involved in avoiding cross-infection should be defined.

Medicine and the Law

Death Following Tonsillectomy

AT an inquest in North Wales on Jan. 23 [1] the jury returned a verdict of "death aggravated by lack of care" in the case of a 5-year-old who had died in hospital the day after tonsillectomy.

The surgeon who operated on the boy said that after the operation, at 12.30 P.M., his condition was satisfactory. At 10 P.M. the surgeon received a report that the boy had vomited blood and had a rapid pulse-rate of 168, but there seemed to be no further bleeding. He asked to be informed if the pulse-rate did not settle down, but he received no further message.

A nursing sister said that at 9 P.M. on the evening of the operation the boy vomited blood, and she called another doctor, who treated the boy; his condition improved. She checked the pulse half-hourly, and at 5 A.M. he was chirpy and asked for his breakfast. She gave him orange juice. Later she saw that the child's condition had deteriorated; the pulse-rate did rise, but not above 168, at which level it was when the doctor called at 9 P.M. and first took it.

A pathologist gave evidence that death was due to heart-failure resulting from reactionary hæmorrhage.

1. *Western Mail*, Jan. 24, 1959.

Public Health

MENINGOCOCCAL MENINGITIS
A FAMILY STUDY

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MENINGOCOCCAL meningitis, even in non-epidemic years, is one of the chief causes of death in the infectious-diseases group. In 1952 the number of deaths per 100 notifications of meningococcal meningitis in the London area was 21·9 (Ministry of Health 1953). The following year this disease was the second commonest cause of death in this group, being exceeded only by poliomyelitis.

Unfortunately the disease is commonest in young children. Beeson and Westerman (1943) found that 45·5% of the victims were children under 15 years. Commenting on meningococcal infection, the Registrar General (1954) states:

"The case fatality is high (25%) and has persisted at that level in recent years despite advances in antibiotic treatment owing to the fact that in many cases the rapid progress of the disease restricts the opportunity for effective intervention . . . In 1950, 208 out of 283 deaths were children under 5 years and 103 were in the first year of life. Apart from those who die there is a further large proportion of cases where the disease leaves a legacy of serious disability."

An analysis of 109 cases of meningococcal meningitis admitted to Booth Hall Children's Hospital in 1950–55 showed that 58 (53%) were under 1 year of age, and that 36 (33%) were aged 1–4 years; the youngest case was in an infant of 2 months. There were 8 deaths in this series (7%).

In view of the extent of this problem, it is surprising that the endemic disease in childhood has not been investigated as fully as that in adults (particularly in the Armed Forces).

Material and Methods

25 proved cases of meningococcal meningitis in children below the age of 4 years were studied.

The organism was isolated from the cerebrospinal fluid, and typed. Swabs then were taken from the nose and throat of intimate family contacts, and, if *Neisseria meningitidis* was isolated, the organism was typed. The occupations of relatives, living accommodation, and cleanliness of the home were investigated.

As a control series, pernasal and throat swabs were taken from a random sample of parents visiting the hospital.

Cerebrospinal Fluid

The cerebrospinal fluid (C.S.F.) was centrifuged at approximately 1500 revs. per minute for ten minutes, the supernatant fluid being used for biochemical investigations.

Part of the deposit was gram-stained, and, if gram-negative diplococci were seen, the remainder of the deposit was inoculated on to chocolate-agar plates and incubated in an atmosphere of 10% carbon dioxide for two days at 37°C. If organisms other than these were seen in the gram film, they were cultured on appropriate media.

Nasal Swabs

Samples of the nasopharyngeal flora were collected by means of a pledget of cotton-wool tightly whorled around the end of thin nichrome wire. Swabs were inserted into each nostril and passed deep into the nasopharynx; they were then cultured on to chocolate-agar and incubated as above.

Throat Swabs

One throat swab was taken from each case and plated out on to chocolate agar and treated similarly to the nasal swabs.

All the swabs were taken by one of us so that uniformity of sampling could be maintained.

Identification of the Organism

Gram-stained films were prepared from each suspected Neisseria colony. If this showed gram-negative diplococci, then the remainder of the colony was transferred to a chocolate-agar plate and incubated at 37°C in 10% carbon dioxide for two days. The organism was then subcultured until a pure growth was obtained, and this strain was kept alive by frequent subculture.

Fermentation tests were carried out on this pure culture using Hiss's serum-water sugars. Each strain was inoculated into a set of four sugars—glucose, lactose, maltose, and sucrose—which were incubated for two days at 37°C in a large glass jar, the screw caps of the Bijou bottles being adjusted to allow gaseous exchange.

After excluding other members of the Neisseria group (particularly *N. flava* i, ii, and iii) organisms fermenting glucose and sucrose were typed by agglutination, using standard group sera and appropriate controls. A colony of the smooth phase was emulsified in saline solution to the opacity of a Brown's tube no. 5 and the tube method with incubation at 55°C was used.

No attempt was made to subdivide group II into group IIA; organisms which were agglutinated by group II sera were designated group II; organisms agglutinated by group-I sera were called group I.

The group-I organisms agglutinated to a titre of 1/250, but the group-II organisms varied in titre, some being 1/125 or even one tube below this; despite the low titres, these organisms were classified as belonging to group II.

The slide-agglutination method was used in the preliminary stages but this did not prove to be of any value.

No studies of the virulence of the organisms or resistance of the host were performed; blood-cultures were not attempted.

Results

The Carrier State

Of the 25 families examined, in 17 one member at least, and often two or three, were found to be carriers of *N. meningitidis*, while of the control families only 4 included carriers:

	No. of families	*Meningococci isolated*
Case contacts	25	17
Controls	25	4

These two groups are not strictly comparable as the contact group is much larger, containing children and other relatives as well as parents. If parents alone are considered then the results are as follows:

	Meningococci	*No meningococci*
Case-parents	13	6
Controls	4	21

These figures are statistically significant: $P = 0.001$.

In the first 7 cases the meningococcus was not typed; of the remaining 18 cases, 17 were group II and only 1 group I. In all the contacts the same group of meningococcus was isolated as from the case. In the single group-I case, all the three members of the family carried a group-I organism.

The finding that the group-II organism was the infectious agent in most of the cases accords with previous studies of the endemic disease.

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Of the 13 contact couples where *N. meningitidis* was isolated, in 8 the organism was found in the father alone and in 1 in the mother only; in 4 cases both parents carried the organism.

Seasonal Incidence

It is generally thought that there is seasonal variation in the cases of meningococcal meningitis, and that the number of cases increases during the winter months. In our series the admission figures for meningococcal meningitis and all acute respiratory infections to this hospital from January, 1954, to January, 1955, were as follows:

Months	*Acute respiratory infections*	*Cases of meningococcal meningitis*
Jan.–March	138	7
April–June	113	6
July–Sept.	53	6
Oct.–Dec.	106	5

These figures indicate that, instead of a winter peak, the cases are evenly distributed throughout the year. Figures for the past five years also showed no seasonal fluctuation.

Distribution by Social Class

The incidence of the disease according to the social class of the father was studied. The proportion of cases falling into each social group is compared with the proportion in each class in Manchester county borough in the 1951 census:

Class	*Population (%)*	*No. of cases (%)*
I (professional)	2	0
II (intermediate)	12	9
III (skilled workers)	55	59
IV (partly skilled)	14	23
V (unskilled)	17	9

Although the number of families studied (25) was not large, these figures suggest that the distribution of meningococcal meningitis is roughly equal throughout the population and shows no predilection for the lower social classes, as was previously supposed.

Housing Conditions

The home conditions of all cases were investigated by a health visitor with reference to overcrowding and cleanliness. Every family visited lived in a house of their own, and only 7 were classified as overcrowded on the basis of 1·5 persons per room. 3 houses were reported to be damp and 4 dirty, but the remainder were clean and well managed. These facts are not consistent with the previous association of meningococcal meningitis with overcrowding and bad housing conditions.

Sex-distribution

In the cases considered the sex-distribution of the disease was equal (12 males, 13 females). This is in agreement with the majority of previous studies, although Fan (1944) found that in epidemic periods the attack-rate in males was twice that in females.

Discussion

The importance of overcrowding in the spread of the epidemic disease in troops was stressed by Glover (1920). Dudley and Brennan (1934), however, working at Chatham Naval Hospital, found no constant relationship between the density of the population and the carrier-rate. In agreement with the latter, Norton and Baisley (1931) in the Detroit epidemic of 1928–29 found no association between the degree of overcrowding in the home and the contact carrier-rate. The results of Rake (1936), which demonstrated the lability of the nasopharyngeal flora, also tended to diminish the importance of the carrier in disseminating disease. The present study suggests, however, that the carrier state is of importance in the spread of meningococcal meningitis in children.

Other factors undoubtedly play a part in the causation of meningococcal infections. All the cases studied were in the youngest member of each family, and the majority were infants. In all probability these babies had not previously encountered the organism and a state of immunity had not developed.

None of the infants was an undernourished, weakling child, nor was there any other simultaneous disease; all were seemingly healthy and well fed. Nutritional deficiency appeared to play little or no part in their liability to infection.

An important factor in the causation of meningococcal infection thus appears to be host susceptibility; environmental influences other than the significant carrier state in the older members of the family appear to be of less importance. The virulence of the strains of *N. meningitidis* isolated was not studied, although it may have been increased either by family passage or by the spontaneous development of a mutant strain.

Measures taken to prevent the disease in the home are unsatisfactory. Detection, segregation, and treatment of carriers is of little general use but may be helpful in some cases. Sulphamezathine (1 g. six-hourly for five days) was given to the fathers of two separate households in which a second case, not included in this study, had occurred, and, despite the presence of further susceptible children, no other instances of the disease developed; but the number of cases is too small to draw definite conclusions as to the effectiveness of this prophylactic treatment. A suitable immunising agent may reduce the risk of clinical attack in susceptible children, and early diagnosis and adequate treatment may also help to prevent spread (Macrae 1955).

Summary

Study of 25 cases of meningococcal meningitis in children below the age of 4 years led to the following conclusions:

1. Meningococcal meningitis in children is associated with a high carrier-rate among contacts.
2. The endemic disease shows little seasonal fluctuation and no difference in sex-distribution.
3. Meningococcal meningitis occurs equally throughout all classes of the population, and overcrowding or bad housing conditions do not influence its incidence.
4. Prophylactic sulphonamide may help to prevent further cases in the household.

We are grateful to Dr. A. Holzel, Dr. W. H. Patterson, and the late Dr. F. Duran Jorda for help and encouragement; to Dr. L. Parker for advice; to Mr. J. Hill and Mr. T. Walsh for technical assistance; and to Miss Rowarth, the health visitor who visited every family in the survey.

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Influenza

In England and Wales the incidence of respiratory diseases has so far this winter been much lower than in the corresponding period of last winter, when epidemic influenza was still prevalent. In the week ended Jan. 17 a few localised outbreaks of acute respiratory disease were reported from widely separated parts of the country; laboratory investigations are

proceeding. There has been an increased demand for hospital beds in London for patients with bronchitis and pneumonia. Increased new claims for sickness benefit have been reported from several Ministry of Pensions and National Insurance offices in Scotland, the north of England, and Wiltshire.

Influenza-virus A (Asian type) has been isolated from a fatal case of pneumonia in the north-western region. This is the first reported isolation of influenza virus in England and Wales this winter.

Vital Statistics for 1958

Provisional figures issued by the Registrar-General [1] show that in England and Wales last year the birth-rate was 16·4 per 1000 population; this is the highest rate since 1949 (16·7). The infant-mortality rate was 22·5 per 1000 live-births—the lowest annual rate ever recorded in this country. The death-rate was 11·7 per 1000 population, compared with 11·5 in 1957 and 11·7 in 1956. The surplus of births over deaths registered in 1958 was 221,531—the biggest surplus since 1949. The still-birth-rate was 21·6 per 1000 total live and still births.

Special Articles

NURSES MALDISTRIBUTED?

THE shortage of nurses in some hospitals, and their uneven distribution, has been investigated by a subcommittee of the National Consultative Council on the Recruitment of Nurses and Midwives,[2] whose findings are commended to hospital authorities by the Ministry of Health.

A recent analysis of the number of nurses and midwives in comparable hospitals in teaching and non-teaching groups shows that the teaching hospitals are much more generously staffed than the non-teaching hospitals, and that the London undergraduate teaching hospitals are appreciably better staffed than their provincial counterparts. The disparity is greatest in the case of student nurses, though still considerable in the case of trained nurses.

Because of the necessary emphasis on teaching and research in the teaching hospitals, the subcommittee thinks that there is some justification for this group having more nurses than non-teaching hospitals, but the difference is greater than their needs demand; and there is no reason for the staff differences between the London and provincial teaching hospitals.

The subcommittee came to the conclusion that the best way to ensure a more equitable distribution of nurses within the hospital service is by persuasion, by encouraging good staff relations, and by improving working conditions in those hospitals with the greatest shortages of staff. Hospital authorities should consider the planning of a complete programme for the 3 years of training so that students would know from the beginning when they are to be on day or night duty, when they will be studying, and when their holidays will fall. There should be suitable recruitment propaganda and appropriate guidance on careers in nursing, especially for those students who intend to train in midwifery.

The subcommittee is in agreement with the General Nursing Council's proposal for the wider grouping of training hospitals and the extension of facilities for training enrolled assistant nurses, and recommends general adoption of the practice of seconding student nurses to hospitals outside their training groups for special experience; these schemes should have a valuable long-term effect on the distribution of nurses.

While it does not advise that the number of nurses employed by teaching hospitals should be restricted as a means of correcting maldistribution, it would like some teaching hospitals to train fewer student nurses and create a better balanced team by employing more enrolled assistant nurses and nursing auxiliaries. It holds that an obligation to serve wherever required in a national nursing corps or within a particular group of hospitals would be difficult to operate, unacceptable to the nurses, and against the best interests of the profession as a whole.

HOSPITAL MIDWIFERY UNATTRACTIVE?

There are problems peculiar to midwifery in hospitals. On the average there is no shortage of pupil-midwives, and many maternity units are fully staffed; but some have not enough nurses to cope with the increasing number of hospital confinements. Where there are shortages, the main reason seems to be that qualified midwives are unwilling to accept service in hospital as a career; the inadequate salary and very limited scope for promotion may be factors.

The solution of this problem, in the opinion of the subcommittee, lies in making the practice of midwifery in hospitals more attractive; particular attention is drawn to the desirability of the midwife having responsibility for individual patients throughout their stay in hospital as opposed to the system of full-time work in the antenatal wards, the labour ward, or the lying-in wards. Pupil-midwives, who are all over 20 years of age, should be treated as adults and not subjected to unnecessary rules or restrictions.

GAMMA-GLOBULIN

GAMMA-GLOBULIN, prepared from pooled plasma from healthy adults by the Lister Institute for the Ministry of Health, is distributed to doctors in England and Wales through the Public Health Laboratory Service—for the protection of susceptible contacts of measles, rubella, and poliomyelitis. Particulars are given in the January issue of the *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service*, as follows:

Measles.—(1) For control of hospital and institutional outbreaks. (2) For persons with intercurrent illness or living in a poor environment for whom measles would be dangerous. (3) For attenuation in children under 3 years of age.

Rubella.—For women exposed to infection in the first 4 months of pregnancy.

Poliomyelitis.—(1) For nurses and medical students, closely associated with early cases, who have not been in known contact with the infection. (2) For babies in a hospital or maternity home exposed to infection soon after birth. (3) For children in a hospital ward where a case has developed—especially those who have recently undergone tonsillectomy.

In addition, gamma-globulin prepared from the blood of persons recently vaccinated against smallpox is held for the treatment of generalised vaccinia or of accidental vaccinal infections endangering the eye, and, in special circumstances, for the protection of unvaccinated smallpox contacts.

This notice first appeared in the *Bulletin* for February, 1956, and in *The Lancet* of March 17, 1956. The prophylactic dose for rubella has now been increased to 1·5 g. in accordance with modern practice.

1. Registrar-General's weekly return no. 2, 1959. H.M. Stationery Office. Pp. 20. 1s. 6d.
2. Distribution of Nursing and Midwifery Staff. Ministry of Health: N.C.C. 17.

In England Now

A Running Commentary by Peripatetic Correspondents

THERE is a fascination in holes. I met a young man the other day bright-eyed and bursting to tell someone that he had been in a subterranean passage. And I can remember the joy with which I used mentally to enter my doll's house through French windows, which led to the diningroom. I had to put my eye down to about 3 in. from the floor and gaze in. There was a hatch to the kitchen and a door opening to the hall, but they only added to the miniature reality and did not spoil the isolation of the retreat. There were penny chairs, a sixpenny table (made in Germany), and a less good piano. While I contemplated the secret treasures, a tiny vase, a silverlike teaset, and the tinsel embers in the fireplace, I had the confident feeling that no grown-up would come down to look too. That encirclement of space was all my own and I was withdrawn from the outer world however many other people were about. All this came back to me the other day as I sat for an hour or more while someone continually titivated the hole in my tooth. He had his mirror and light and gazed in silence into the cavity. Was he allured by a chamber no-one else could see? I have often wondered what makes people choose to be dentists; perhaps at last I have stumbled on the answer.

* * *

Of all the hospitable races on this great Earth there must surely be few so welcoming as the Indian; a fact that made my 3-odd years of peripateticism there very pleasant. Scarcely a statesman touched down at Delhi airport but was driven garlanded through triumphal arches erected hastily by the public works department—whether he was Bulg and Krush, Nixon, Foster Dulles, Bevan, Premier Whang-ko-ping of one of the smaller Pacific Islands, or Frank Buchman. All such visits were hailed by the press of the country concerned as a triumphant demonstration that the Indian People were right behind whatever it was the press hoped they were right behind. It never did mean that of course, but it meant that Indians were really very pleasant people and enjoyed putting on a show.

This is not to denigrate the wonderful reception given to Prince Philip, which does seem to have been a little outside even the extraordinarily rapturous standards of past years—perhaps because his easy informality is just what Indians like best. However, be all that as it may, the news of his watching the moon rise over the Taj Mahal caused a flood of nostalgia to overwhelm this peripatetic breast: the cool autumn night of 1954, the ghostly gleaming silhouette, the watchman's glowing lantern deep within the sepulchre, the stars twinkling in the ornamental pools. It is an axiom among Indophils that, however much rapture one may have endured from chronic tourists, one's own first visit is never disappointing. And so it was with us; and thanks to the quietude of the moment, and a 15-minutes at f.2, the magic experience has been immortalised for us on 'Kodachrome'. Which was bad luck on the Duke really, because a visit to the Taj is an experience which must be somewhat diluted by the presence of several dozen journalists flashing bulbs, and a cheering throng of several thousands. Though we ourselves were not greeted at Jaipur by elephants with painted trunks, nor (unfortunately) presented with ruby-encrusted gifts, there *are* advantages in being ordinary.

* * *

I was interested in my peripatetic colleague's Nobel prize project (Jan. 17), but I think that the problem of locating Meckel's diverticula is capable of a less cosmic solution. And as the recent Pasternak affair has cooled my own ambitions, I readily offer him my suggestion. I believe our old friend the *Tænia solium*, already familiar with the habitat, could be specially trained for the purpose. It should only be a matter of inducing a few conditioned reflexes, though it would be an advantage to employ one that had already enjoyed as a host an experienced diplomat accustomed to exploring every avenue. A worm so conditioned, and equipped with a simple meckel-speculum, should be able to traverse and explore the passage with ease; the final deductions being collated afterwards, of course, from the tape recordings.

* * *

Some time ago, when I was a house-physician, I decided to buy a scooter. I had no idea how to ride one, but a consultant on the staff possessed a 70 c.c. model, which he'd bought because his wife always wanted the car, and allowed me to try it. Cautiously I let in the clutch and wobbled round the hospital paths, cheered by my colleagues. It seemed easy enough; but I felt a larger machine might be more headstrong, so I arranged to buy one of the same sort.

Eventually the day arrived when I was to collect my scooter. The man at the shop gave me a few hints before I pushed it into Regent's Park for a trial run round the Outer Circle. Having covered several hundred yards safely, I became perhaps over-confident, and imagined that stopping would be as easy as starting. I was wrong. They didn't seem very surprised to see me at the shop when I pushed the bike back to have the shattered windscreen removed; and one youth remarked that he always advised beginners to ride without a screen.

I got the bike back to the hospital in the end. It took rather a long time because I didn't dare defy the mighty roar of London's traffic by turning right, and had to go by a lengthy and unfamiliar route. For days the scooter stood outside the hospital, admired by all. It soon had quite a few miles on the speedo, since everyone in the place had a go on it. Everyone, that is, except me. It took me time to regain my courage; but once I had done so I became fascinated by the little machine and was soon darting about in front of buses and creeping up at traffic lights as to the manner born. I even passed my driving test first time.

Now I have a 125 c.c. model which, since the wards at my present job are far apart, I use to do my rounds. The male members of the staff are most helpful when it comes to minor repairs, although my carefully built-up reputation of feminine helplessness was almost ruined when I incautiously revealed that I knew how to change the plug. It's a pleasant machine; but I was reading about the new ones, 175 and 200 c.c. jobs . . .

* * *

About three weeks before, I had a disc removed by a surgical colleague, and I was shaving. It was my wife who spotted it first. She said, "You're getting varicose veins in your right leg." I paid no attention whatever. "Rubbish", I said.

After a hot bath 48 hours later, which presumably increased the blood-flow and loosened the clot in the thrombosed leg, I found myself intensely breathless. My pulse went up and I suppose my blood-pressure fell, for fortification spectra appeared for some 15 minutes though no headache followed. I experienced what the textbooks describe as "a sense of dissolution". I think now that this is a very good description. When my family doctor arrived, I was better and even suggested the right diagnosis. Though the X-ray was clear, it was curious to experience a sense of oppression clearly localised in the left side of the chest, a sense of oppression that later disappeared almost suddenly.

At any rate, I reflected, as the first candidate approached our table, there cannot be many who have examined in the Membership with a prothrombin-time only 25% of normal.

* * *

The children have been attending Sunday school for several weeks now, and one of the stories told to them was that of Jesus and the lepers. There was, of course, some confusion at first between leopards and lepers, but this was soon resolved by the simple answer that the former had spots and the latter sores. It was not so easy to answer Alison's question a few weeks later: "I can understand how the second leper got leprosy, Daddy, but how did the first one get it?"

The climax came the other week, when I overheard the following conversation:

Alison (aged 6): James! There's something the matter with my dolly. Will you have a look at her?

James (aged 4, pretending to be the doctor): Well, she's got sores. It must be leprosy. But never mind, Alison, because Jesus will make her better.

Alison (after a pause): Unfortunately, Jesus isn't on duty today.

Letters to the Editor

SUPPLY AND DIETARY USE OF FATS

SIR,—It is encouraging to note Dr. Irvine H. Page's recent conversion, indicated in his letter of Jan. 17, to the importance of an increased dietary use of unsaturated vegetable oils to regulate serum-lipids.

His earlier work [1] had led him to think that any difference in this respect between animal and vegetable fat had " proved an illusion ", but his recent paper [2] confirms the results of Kinsell, Ahrens, and many others frequently published in your columns. Not long ago, Page and his colleagues concluded [3] that " the evidence at present does not convey any specific implications for drastic dietary changes, specifically in the quantity or type of fat in the diet of the general population, on the premise that such changes will definitely lessen the incidence of coronary or cerebral artery disease "; they dismissed my claims [4] as " highly speculative . . . Sinclair's estimates of the composition of western European diets led him to conclude that they are indeed marginally deficient in unsaturated fatty acids, but more recent evidence does not support this estimate ".

There is still no *proof* that alteration in the quality or quantity of dietary fat will affect the incidence of atheroma or of ischæmic heart-disease, but there is abundant circumstantial evidence that the incidence of both is increased by a relative deficiency of certain highly unsaturated fatty acids, usually referred to as essential fatty acids. If we are to increase the dietary use of unsaturated fats, and if (as Dr. Page suggests) there is a problem of supply, we must be clear which ones are the most desirable, considering their effect on serum-lipids, as well as their palatability, stability, and availability.

In the same issue Dr. Ahrens with his colleagues records a very interesting study on two patients to support his view that the effect of dietary fats on serum-lipids depends upon " the net unsaturation of the dietary fat " and not (as Dr. Kinsell and I believe [5]) upon the content of essential fatty acids (E.F.A.). I fear his work does not settle this question.

NATURE OF ESSENTIAL FATTY ACIDS

We must be clear about the meaning of our terms. Years ago I concluded [6] that an essential fatty acid was a nutrient which was " defined as a specific chemical substance that cannot be synthesised by the body in sufficient amount and must therefore be provided in relatively small amount unless a closely related substance is available to the body, since it or a closely related substance is essential for the bodily processes of metabolism, growth or repair ". That is good enough as a definition, but the term " essential fatty acid " is bad: it is long and not exact, since not all of these nutrients are acids; undoubtedly the old term " vitamin F " [7] is preferable for this class of nutrients.

The requirement of nutrients depends on the existing conditions: thiamine (vitamin B_1) is required for oxidising pyruvic acid which comes from dietary carbohydrate (it is also needed for oxidising α-ketoglutaric acid which occurs in Krebs' tricarboxylic-acid cycle); therefore the dietary requirement of thiamine is increased if much sugar is eaten. If one or more of certain highly unsaturated fatty acids (or phospholipids or alcohols) are required for health in man and cannot be synthesised in the body in sufficient amount to maintain health in the existing conditions (as for instance a diet relatively high in more saturated fatty acids or inactive isomers of the required fatty acids), then those highly unsaturated fatty acids are by definition essential fatty acids, even though some may be more efficient than others in preserving or creating health. It is irrelevant to the characterisation of E.F.A. for man whether or not a fish oil prevents a scaly tail in rats or even promotes their growth (and unless paired-feeding is used the failure of growth may merely indicate the rat's distaste for fish oils). It is also irrelevant whether certain essential fatty acids are also needed for other purposes in man, such as preventing certain skin lesions; in this respect the analogy with different uses of thiamine is helpful. Further, a chemical formula cannot necessarily predict whether a fatty acid is or is not an essential one for man. Indeed, James and Lovelock [8] have very recently concluded that " It has yet to be proved that any . . . human disease is due to a deficiency of essential fatty acids ". It might be supposed, therefore, either that every human always receives sufficient in his diet to prevent disease, or that no fatty acids are nutrients for man; Hansen and his colleagues [9] have disproved both these possibilities.

To avoid the error of equating raised serum-cholesterol with atherosclerosis I was careful in my first communication to you on this subject [4] to discuss a relative dietary deficiency of E.F.A. in relation to atherosclerosis and coronary heart-disease rather than in relation to serum-cholesterol. I was particularly concerned to stress the importance of the dietary ratio of E.F.A. to non-E.F.A., which is what I meant by *relative* deficiency.

Years ago Dr. Basnayake and I found [10] that a rat on a fat-free diet develops the skin lesions of E.F.A.-deficiency and accumulates sterols in its epidermis even though its serum-cholesterol is abnormally low; this deposition of lipid in the epidermis we believed to be analogous to the deposition in the intima, as I have discussed elsewhere.[11] If non-E.F.A. (e.g., hydrogenated coconut oil) are added to the diet, more epidermal sterols accumulate and the serum-sterol is abnormally elevated, and this occurs even if some E.F.A. are added to the diet. A pure dietary deficiency produces a low serum-cholesterol, and a relative deficiency (that is, a high dietary ratio of non-E.F.A. to E.F.A.) causes a high serum-cholesterol; the serum-E.F.A. need not necessarily be low since the important factor is probably the high ratio of non-E.F.A. to E.F.A. in the environment of the enzymatic esterification of cholesterol so that cholesterol is esterified with unusual fatty acids rather than with the usual highly unsaturated ones.

The same may well be true for man: phrynoderma in man we believe to be analogous to pure E.F.A.-deficiency in the rat,[12] and I have been privileged to see some recent unpublished Indian work which shows that serum-cholesterol and serum-linoleic-acid are low in this disease; but a relative deficiency (a high ratio of non-E.F.A. to E.F.A.) may cause I believe atherosclerosis and ischæmic heart-disease, and tends to be accompanied by raised serum-cholesterol, and I have discussed elsewhere [11] the way in which this single dietary factor could cause these two distinct conditions. Of course the particular E.F.A. that are most effective in lowering serum-cholesterol are not necessarily those that are most effective in curing phrynoderma: arachidonic acid (C_{20} and 4 double bonds) is more effective than linoleic acid (C_{18} and 2) which is more effective than various more highly unsaturated C_{22}-acids for the growth of rats [13]; but these last acids might be more effective than linoleic acid, and this than arachidonic acid, in lowering serum-cholesterol in man. In rats the level of serum-cholesterol under certain experimental conditions does not follow the net unsaturation of the fatty acids [14]: cottonseed or corn oil (both rich in linoleic acid) gave lower serum-cholesterol levels than did coconut oil or butter or hydrogenated cottonseed oil, but

1. Page, I. H. *Circulation*, 1954, **10**, 1; Page, I. H., Lewin, L. A., Gilbert, J. *ibid.* 1956, **13**, 675.
2. Brown, H. B., Page, I. H. *J. Amer. med. Ass.* 1958, **168**, 1989.
3. Page, I. H., Stare, F. J., Corcoran, A. C., Pollack, H., Wilkinson, C. F., Jr. *Circulation*, 1957, **16**, 163.
4. Sinclair, H. M. *Lancet*, 1956, i, 381.
5. Kinsell, L. W., Sinclair, H. M. *ibid.* 1957, i, 883.
6. Sinclair, H. M. *Biochem. Soc. Symp.* 1952, **9**, 80.
7. Evans, H. M., Burr, G. O. *Proc. Soc. exp. Biol. N.Y.* 1927, **25**, 390.
8. James, A. T., Lovelock, J. E. *Brit. med. Bull.* 1958, **14**, 262.
9. Hansen, A. E., Adam, D. J. D., Wiese, H. F., Boelsche, A. N., Haggard, M. E. *Proc. 4th int. Conf. biochem. Probl. Lipids* (Oxford), 1958, p. 216.
10. Basnayake, V., Sinclair, H. M. *Proc. 2nd internat. Conf. biochem. Probl. Lipids* (Ghent), 1956, 476.
11. Sinclair, H. M. *in* Lectures on the Scientific Basis of Medicine; vol. vi, p. 260. London, 1957.
12. Ramalingaswami, V., Sinclair, H. M. *Brit. J. Derm.* 1953, **65**, 1.
13. de Iongh, H., Thomasson, H. J. *Nature, Lond.* 1956, **178**, 1051.
14. Hegsted, D. M., Andrus, S. B., Gotsis, A., Portman, O. W. *J. Nutrition*, 1957, **63**, 273.

the highest values were obtained with tung oil which is rich in eleostearic acid (an isomer of linolenic acid, C_{18} with 3 double bonds).

If Ahrens' net-unsaturation hypothesis is correct, then eleostearic and linolenic acids should lower serum-cholesterol equally and more efficiently than linoleic acid; and the isomers of linoleic acid (such as the geometrical *trans* isomers which are found in the body-fat and milk of ruminants—e.g., cows and sheep—and in some margarines) should be just as effective as the ordinary acid found in most vegetable-seed oils. Certainly this is not the case with growth or the cure of skin lesions in E.F.A.-deficient rats or mice or with serum-cholesterol levels in rats, and it is difficult to see why, if net unsaturation is the only relevant factor, serum-cholesterol in man should be raised by hydrogenated whale oil (iodine number 83 and no linoleic acid) and lowered by olive oil (iodine number 86 and about 7% linoleic acid).[15] I still prefer to believe, on all existing evidence, that in the prevention of atherosclerosis and ischæmic heart-disease the structure of highly unsaturated fatty acids is important. We are concerned with the ratio of favourable fatty acids to unfavourable fatty acids, and with the structure of the acids in each group (since this determines the degree to which they are favourable or unfavourable), and we are not concerned merely with net unsaturation.

Even if the lowering of serum-cholesterol were a function solely of net unsaturation, this would not disprove the hypothesis of a relative deficiency of E.F.A. being concerned in atherosclerosis, since, as Dr. Ahrens will readily agree, the ability of something to lower serum-cholesterol is not necessarily relevant to its ability to prevent atherosclerosis. This is particularly important when certain drugs are appearing on the market for the lowering of serum-cholesterol; in lower animals they do so by inhibiting synthesis of cholesterol, and they may also cause severe adrenal damage and death.

PRACTICAL STEPS

So those who have seen—and also read correctly—the writing on the wall are not merely concerned with lowering serum-cholesterol or with the supply of unsaturated oils. After my first communication [4] Dr. Keys accused me in your columns [16] of making the irresponsible suggestion that "we solve the coronary problem, without retreating from our high-fat diet, by taking a daily swig of linoleic acid". Others may have read my communication less frivolously. We all wish to obtain our nutrients from foods rather than from pharmaceutical preparations; but, until we know more about the factors involved, some hypercholesterolæmic men with a family history of ischæmic heart-disease are prepared to include daily in their diets 2 oz. of unhydrogenated vegetable-seed oil to keep their serum-cholesterol low. Certain firms have introduced excellent foods very rich in E.F.A.: 50 g. of corn oil (supplying about 28 g. of linoleic acid) is obtained by the use of a pint of 'Alfonal' milk, 1 oz. of their milk powder, 1 oz. of their margarine, and 1 oz. of their cheese spread. We can indeed modify our diets to raise the ratio of E.F.A. to non-E.F.A.

But we still urgently need more knowledge. Dr. Ahrens and seven colleagues have made their observations on two volunteers, and he would be the first to agree that this is too few. But, as you have so rightly emphasised,[17] this essential medical research could not be done on even one volunteer in this country because the facilities do not exist. Therefore the emigration noted recently in your columns is perhaps as great amongst workers in human nutrition as in any other branch of medical research: not long ago someone who had done promising work in one of our many institutions for animal nutrition, but wanted to work on human nutrition, migrated; and he is now a full professor in the United States, a land flowing with milk and money. (But perhaps only temporarily so, since its rate of population increase is amongst the highest in the world.) With world population doubling itself every fifty years and two-thirds of it already underfed, and with much of the more prosperous part wrongly fed, the problem of human nutrition is the greatest confronting us: those with vision who have seen this have recently included Sir Henry Dale [18] and Sir Julian Huxley [19]; and Sir Charles Darwin in his Rede [20] and Herbert Spencer Lectures before the Universities of Cambridge and Oxford has shown how vastly more devastating is this problem than that of the hydrogen bomb.

Undoubtedly one important contribution to its solution is to increase the world supply of vegetable-seed oils, such as soybean and sunflower. A second is to incorporate these into foods. This can be done in a variety of ways—e.g., by adding them to skimmed milk (much of which is at present wasted) to give an adjusted milk that is almost a perfect food for man. Such a non-dairy milk is being made in various parts of the world, including this country, but is now threatened here with most serious obstruction. In the House of Commons on July 10, 1958, Mr. Peyton, member for Yeovil, asked the Minister of Agriculture, Fisheries, and Food whether "he does not think that the increasing use of milk substitutes would constitute a very serious threat to the dairy industry? Does he not think that to apply the names 'milk' and 'cream' to some of these substitutes is an outrageous and, indeed, offensive breach of the inalienable copyright of the cow?". The Minister, who happens to be a dairy-farmer though everyone is sure this does not influence his decisions, replied that he had considerable sympathy with what Mr. Peyton said and assured him that he was as anxious as Mr. Peyton was that the industry should be properly protected.[21] All members of the medical profession, and most mothers (although unfortunately a decreasing number), will contest the cow's alleged copyright, as would both St. Paul [22] and Shakespeare.[23].

Since *salus populi* is not now *suprema lex*, we must not be surprised if the interests of the dairy industry are put before those of the population, but it is difficult to see in what way this great industry is threatened. (It does not appear to be disastrously threatened by the important and increasing ice-cream industry.) An adjusted milk uses about 95·5% of the dairy milk, and all otherwise wasted separated milk can be used for this purpose.

CONCLUSION

We may conclude, then, that the evidence at present indicates that abnormally raised serum-cholesterol can usually be lowered by reducing the dietary ratio of saturated to unsaturated fat, and that the structure of the fat in each group is relevant—rather than the mere number of double bonds—so that we are justified in speaking of essential fatty acids (or vitamin F). It is possible to make this alteration in diets by including unhydrogenated vegetable-seed oils, but recent proposed legislation will greatly discourage this desirable change. An adjusted milk made by adding certain vegetable-seed fats to separated cow's milk is an excellent food for this purpose, and can play an important part in the nutrition of both privileged and underprivileged countries of the world. By suitable manufacture or animal feeding, essential fatty acids can be increased in our diets at the expense of undesirable ones in such foods as margarine, pork, bacon, lard, eggs, adjusted cow's milk, and cooking oil. Many fish are excellent sources of essential fatty acids, but the fat of beef and mutton is not, although by research this defect may become manageable. The tendency in the diets of the most privileged countries over the past decades has been increasingly in the opposite direction: by the increased use of hydrogenated fats, of butter from stall-fed cows, of hard pork and bacon, of hydrogenated lard, and of eggs from battery-fed hens, we have been decreasing the ratio of essential fatty acids to non-essential

15. Malmros, H., Wigand, G. *Lancet*, 1957, ii, 1.
16. Keys, A. *Lancet*, 1956, i, 576.
17. *Lancet*, 1957, i, 977.
18. *New Scientist*, Jan. 1, 1959, p. 5.
19. Huxley, J. New Bottles for New Wine; p. 168. London, 1957.
20. Darwin, C. The Rede Lecture. London, 1958.
21. *Hansard*, House of Commons, July 10, 1958; p. 575.
22. I *Corinthians*, iii, 2.
23. *Macbeth*, I, v, 18; *Romeo and Juliet*, III, iii, 55.

ones and therefore creating a relative deficiency of the former.

There is no proof that the lowering of serum-cholesterol in this way decreases atherosclerosis. There is, however, strong circumstantial evidence that this lowering is desirable, and that the adverse dietary ratio of non-essential fatty acids to essential fatty acids is the most important single factor in the rise in atherosclerosis and ischæmic heart-disease in countries such as this. Proof or disproof could be obtained by a large-scale feeding trial on middle-aged men over several years, and this has been planned in part though considerable funds would be required for it. More research is needed in every aspect of this problem. In the meantime prudent persons, particularly middle-aged men with a family history of hypercholesterolæmia or cardiovascular disease, may well wish to modify their diets, and agricultural economists and planners should consider the world's supply of essential fatty acids in general and of vegetable-seed oils in particular.

Oxford. H. M. SINCLAIR.

MENTAL HEALTH BILL

SIR,—Dr. Atkin (Jan. 24) drew attention to the need for special psychopathic units if the requirements of the Mental Health Bill are to be met.

Such units to be effective would require a highly trained staff and a relatively high staff–patient ratio. Without this there is little doubt that the aggression and general antisocial behaviour of these patients would lead to a feeling of staff frustration and irritation which would make effective treatment difficult or impossible. These units would probably need to limit their patient population to 100 or less for an open unit, and 20 might well prove the optimum number for a severely disturbed population in a closed ward. Group and community methods of treatment are probably the most suitable for these patients. The success of a psychopathic unit will depend on attracting staff whose personalities and training suit them for this work. Such a unit—open, closed, or both—if attached to a mental hospital will inevitably arouse strong reactions in the adjacent hospital and surrounding community. Mental hospitals are enjoying their new-found respectability and will not relish a setback in public relations. Nor will their resident staff approve of antisocial elements in the vicinity of their homes and families.

It is a pity that the word psychopath has come to be associated in the public (and professional) mind with the idea of violent behaviour. Most of the patients diagnosed as psychopaths (and this would also apply to the definition used in the new Bill) do not conform to this sinister picture, but are petty thieves, drifters, minor degrees of sexual perversion and so on.

The situation of the psychopath now might be compared with that of the schizophrenic patient 20 years ago, before physical methods of treatment were introduced. The image of destructive behaviour which the schizophrenic then represented seems now to be found in the public's attitude towards the psychopath. To attract personnel to this work and provide the proper climate for treatment, strong positive sanctions will be needed and the Bill has made a start by implying that the psychopath is ill rather than bad. The present situation affords a remarkable opportunity for the medical profession to mobilise its resources.

Clearly the immediate need is to plan units to use such skills as we already possess and to start research which can begin to fill in the enormous gaps in our knowledge. Otherwise patients will begin to flow to mental hospitals from the courts or from family doctors, and will either be refused admission or be admitted to ordinary wards where they cannot be given the treatment they need and where they will merely repeat unproductively the pattern of their antisocial behaviour.

MAXWELL JONES
FERGUS STALLARD
RONALD BROOKS
ISOBEL HUNTER.

Belmont Hospital,
Sutton, Surrey.

SIR,—I feel that Dr. Heaton-Ward (Jan. 17) is too pessimistic about the possibilities of voluntary admission of subnormal patients over 21, and their treatment in hospital on an informal basis after the age of 25, under the new Mental Health Bill.

While it is true that the unwelcoming appearance of many present mental-deficiency hospitals, combined with their "custodian" approach evolved under the old regulations, militates against this, it is to be hoped that the challenge to adopt a more enlightened and progressive attitude is accepted in the same way that it has been by mental hospitals over the past twenty years. This will require much more clinical work, closer contact between the psychiatrist and the patient, and more active therapeutic programmes than in the past; but the fact that many mental hospitals now have hardly any psychotic patients under certificate surely points the way. Similarly, the informal attendance of discharged patients at properly constituted outpatient clinics, while involving much more clinical work, would seem to be a more fruitful line of approach than prolonged licence under the threatening shadow of enforcable return.

While the problem of persuading the intellectually inferior to recognise their own limitations is not inconsiderable, is it any worse than dealing, for example, with the paranoid schizophrenic under the same regulations?

Lea Colony,
Bromsgrove, Worcs. T. L. PILKINGTON.

SIR,—Many of Dr. Nelson's fears (Jan. 24) about the effect of the new Bill on defectives can be relieved by the results of a survey made recently in Cornwall, Devon, Dorset, and Somerset.[1]

Over five years the proportion of mental defectives successfully discharged averaged 76% per annum. Of 368 failures 74% were within five years successfully relicensed and discharged back to the community. A ten-year follow up of 315 ex-defectives five years after discharge showed that 78% were in employment, 51% had had no periods of unemployment since discharge, 29% were happily married, and 91% had committed no further police offence.

Of consecutive admissions who were over 16 years of age and had an I.Q. above 38, 54% were later returned to the community.[2] Many patients with similar degrees of disorder and dullness became outpatients.

The main conclusions of the survey were:

The proportion of high-grade adult defectives with mental disorder as their main disability varied from 26% to 41%.

Mental disorder was one of several interrelated handicaps which in practice led to certification as defective.

The major component of mental disorder was the group of personality deviations.

The diagnosis of mental defectiveness appeared to overlap that of personality deviation.

Early parental deprivation, adverse childhood influences, and loss of social security were significant causes of both personality disorder and intellectual dullness in early adult life. Since those with personality disorder were by definition socially inadequate, it was not surprising that many were diagnosed (if not certified) as defective.

1. Craft, M. J. Mental Disorder in the Defective, 1958. Royal Institution, Starcross, Devon.
2. Craft, M. J. *Lancet*, 1959 (in the press).

With time and training, many of those who once had personality deviations appeared to have as much community success, in terms of numbers in employment, records of continuous employment, and marriage, as a control series, though they were more likely to be convicted in court.

The drug benactyzine and the use of group psychotherapy improved the rating scores of some groups with personality disorder.

These results agree with the only other, and more detailed, investigation into the association of mental disorder and defectiveness made by Penrose in 1938,[3] and they support the plea he made in 1957 that, because of the fine distinction between the high-grade defective and other mentally ill, there should be one legal code to cover both. Let us not put the clock back.

Balderton, Notts. MICHAEL CRAFT.

SIR,—To those of us with experience of mental-deficiency practice some aspects of this Bill give cause for concern.

Psychopathic and subnormal patients over the age of 21 are denied the opportunity of hospital treatment unless they elect informal status, or are the subjects of a hospital order made by a competent court. It is naïve to imagine that many of these patients have the insight to appreciate the need for care or the will to remain informally in hospital long enough to benefit from therapy. It is therefore an error to put them on the same footing as patients of normal intelligence who may be going through a similar phase of neurotic instability. These subnormal patients—psychopathic and non-psychopathic—may obtain a nebulous freedom of choice at the cost of essential therapy, which they will receive only when drifting delinquency brings them within the ægis of the law.

The elective period of six months for appeal to a mental-health review tribunal is too short a time in which to achieve a therapeutic response, or to encourage cooperation in most patients who are admitted for compulsory treatment. This is particularly grievous when adequate safeguards exist in the statutory review and appeals machinery elsewhere. This criticism also applies to the unduly involved clauses about leave of absence. Too lengthy and too assiduous conditions of "licence" before discharge are to be deprecated, but the personality of the patient and his home circumstances are more cogent considerations than any statutory date-line, however well-meant.

The amendment proposed to the Sexual Offences Act 1956 will leave some subnormal and psychopathic women without even the present legal protection offered to the feebleminded.

Dispensing with the judiciary in admission procedures under part IV of the Bill, and placing responsibility for curtailing the patient's freedom on the doctor, contrasts strongly with the quasijudicial intervention permitted at later stages in the patient's history, welcome though this intervention may be.

The use of the term "responsible medical officer" could be construed as a further stroke towards the death-knell of the statutory medical superintendent. It will almost certainly demand a review of establishments and the creation of more consultant appointments.

Today there is a surge towards informality. But time and a growing appreciation of the uncertain habits of the mentally deficient are likely to bring a reaction, with a return towards compulsory care.

Royal Albert Hospital, Lancaster. ROBERT C. CUNNINGHAM.

AN INDIAN VILLAGE

SIR,—The Indian village described by Dr. Chaudhuri (Jan. 17) is by no means typical. In the first place it is very close to the capital. The number of Hindus in it is very small, and most unusual of all is its wealth. Only about half the families have an income which I would consider usual for a South Indian village. Indeed, this is probably optimistic as the pay of Rs.100 per month is that of a senior laboratory technician or an ordinary schoolteacher. On the whole I would have thought this was a prosperous place. The fact that the level of nutrition is so low shows what must be expected elsewhere.

Women's Hospital, Liverpool. R. E. REWELL.

MEDICAL ASPECTS OF ADOPTION

SIR,—We should like to reply to some of the comments on our article.[1]

We would agree with Professor Illingworth [2] that an alarmist outlook on "brain damage" is to be avoided at all costs; and it was our intention to point out that in adoption procedures a rational approach, based on available knowledge and skills, should be used. It was therefore most encouraging to read Mrs. McWhinnie's description (Jan. 17) of the thorough and understanding approach which is used by the Guild of Service for Women in Edinburgh. The procedure outlined should be a model for us all to copy.

We were in error in stating that literature on adoption was not available to the public, and are grateful to Dr. Hilda Lewis (Jan. 3) for drawing our attention to the excellent pamphlet *Adopting a Child* issued by the Standing Conference of Adoption Societies. We have since read the pamphlet, and our only regret is that it is not more widely distributed. Nevertheless we feel that our failure to encounter this pamphlet previously or to find any informative book on adoption in various libraries is an indication that further efforts are needed to reach the public, both lay and medical.

Royal Hospital for Sick Children, Glasgow. J. A. BLACK
F. H. STONE.

ANTIBIOTICS AND THE COMMON COLD

SIR,—At the suggestion of Prof. L. P. Garrod, I have carried out a series of tests the results of which have a bearing on one aspect of this controversy.

Dr. Ritchie (Jan. 24), replying to the suggestion that if any antibiotic is to be used against the common cold penicillin deserves a trial for this purpose, refers again to the sensitivity tests which he originally reported [3] which were said to show that mouth bacteria are more consistently sensitive to tetracyclines than to penicillin.

These tests were done with proprietary discs, the content of which is 0·5 or 2·5 units (0·3 or 1·5 μg.) of penicillin and 10 or 100 μg. of each of the tetracyclines. This difference in content is perhaps excessive, but some such difference is required because penicillin, owing to its rapid excretion, attains lower levels in the blood than tetracycline. It assumes that treatment is to be systemic, but the suggestion for the treatment of the common cold was that the antibiotic should be applied locally. A valid test of the efficacy of antibiotics so employed should surely compare the effect of equal concentrations. The only correction required in a diffusion test is one for the rate of diffusion: that of tetracycline is slower than that of penicillin by a factor of 47/88—i.e., 0·53.[4]

Our entire present class of students in bacteriology were instructed to make cultures of their own saliva on blood-agar plates containing two cups. These were subsequently filled with solutions of tetracycline and penicillin containing 50 and 26·5 μg. per ml. The radius of the inhibition zones in 40 satisfactory cultures was measured after incubation: those produced by tetracycline varied from 5 to 12 mm. with an average of 9·4 mm., and those

3. Penrose, L. S. *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 299, 1938.

1. *Lancet*, 1958, ii, 1272.
2. Illingworth, R. S. *ibid.* p. 1373.
3. Ritchie, J. M. *ibid.* i, 618.
4. Garrod, L. P. Eight Colloquia on Clinical Pathology. Brussels, 1958.

produced by penicillin from 7 to 19 mm. with an average of 11·7 mm. Small numbers of colonies of more resistant organisms were present in 10 penicillin zones and 15 tetracycline. Mouth bacteria are therefore in fact more sensitive to penicillin than to tetracycline.

Department of Pathology,
St. Bartholomew's Hospital,
London, E.C.1. PHILIP H. N. WOOD.

CANCER

SIR,—Mr. Bertwistle's letter of Jan. 17 leaves out one important way of reaching the public. He makes no mention of the advisory staff of public health authorities who are constantly in close communication with the very public he hopes to educate. Health visitors and home nurses are already available and they are having the simple discussions Mr. Bertwistle is calling for.

There seems to be an idea in the minds of consultants that only a doctor must tell the public about health and disease. In fact consultants are often unable to disentangle professional jargon and everyday language and leave the public more confused and more fearful than before. Some general practitioners will take time to discuss variations in the usual health of their patients but the great majority have not the time to do it properly. It should be realised that mothers will quite readily discuss health matters with a sympathetic and informed home visitor.

The field of cancer education is a good example of cooperation in the health services. Most physicians and surgeons will be only too willing to talk to groups of health visitors and home nurses to ensure that they are informed about cancer. They could quite successfully pass this information on as required.

Health Department,
Barrow in Furness. I. D. M. NELSON
Medical Officer of Health.

SIR,—I agree wholeheartedly with Dr. Donaldson in his remarks last week about education of the public in matters of disease. Also with Emerson's aphorism—Knowledge is the antidote to fear. My contention is that the word " cancer " does not convey knowledge, only fear.

London, W.1. F. D. SANER.

S.H.M.O.s AND THE WORKING PARTY

SIR,—As many S.H.M.O.s will be aware, the Central Consultants and Specialists Committee, in the belief that no satisfactory long-term reorganisation of hospital medical staffing can be planned until medical staffing needs are more fully known, is carrying out a survey hospital by hospital. The committee hopes in this way to form an assessment of medical staffing needs or deficiencies, which it feels will be an essential part of its evidence to the Joint Working Party on Hospital Medical Staffing Structure set up by the Minister of Health and Secretary of State for Scotland in collaboration with the Joint Consultants Committee.

In this connection all hospital group medical committees have been asked to complete a detailed questionnaire, including recommendations on staffing needs. Regional consultants and specialists committees will then collate the forms and forward them to the Central Consultants and Specialists Committee with their comments.

The S.H.M.O.s Group executive committee of the British Medical Association desires me to urge that S.H.M.O.s should encourage their group medical committees, when considering the replies they will make to the questionnaire, to bear in mind the position of S.H.M.O.s. It is generally accepted, not only by the S.H.M.O.s Group but by the Central Consultants and Specialists Committee, that the whole aspect of the S.H.M.O. grade has changed and that it is now an anomaly and should be abolished.

The group executive committee hopes that S.H.M.O.s will cooperate in this matter as a contribution towards the achievement of an improved status and scope for all at present in the grade.

G. WARING ROBINSON
Leicester. Chairman, S.H.M.O.s Group Executive Committee.

SERUM-TRANSAMINASE LEVELS

SIR,—The estimation of serum glutamic oxaloacetic transaminase (S.G.O.T.) activity and of serum glutamic pyruvic transaminase (S.G.P.T.) activity is enjoying an increasing vogue. The determinations are carried out by incubating serum and α-ketoglutarate with aspartate to determine S.G.O.T., or with alanine to determine S.G.P.T.: the techniques of different authors differ chiefly in respect of the temperature of incubation, duration of incubation, and the method by which the rate of the reaction is determined. The rate of reaction is a measure of enzyme activity; unfortunately several units have been proposed for expressing this activity.

(1) Karmen, Wróblewski, and LaDue [1] for both reactions used paper chromatography to isolate the glutamate produced, which was then determined. The results were calculated and reported as μmol of glutamate produced per ml. of serum by incubation for one hour at 37°C under the conditions of the determination.

(2) Karmen [2] determined S.G.O.T. by reducing the oxaloacetate produced by the reaction with reduced diphosphopyridine nucleotide; the progress of the reaction was followed by determining spectrophotometrically the fall in the extinction at 340 mμ. Incubation was at room temperature. One unit was defined as that activity which caused a fall in the extinction coefficient of 0·001, and results were reported in units per ml. serum per minute.

(3) Wróblewski and LaDue [3] used the same method and the same unit for determining S.G.P.T. but specified the temperature of incubation as 23°C.

(4) Steinberg et al.[4] used a method similar to (2) and (3), but incubated at any convenient temperature; by means of a graph the result was then adjusted to a standard temperature of 25°C. Their unit is a decrease of the optical density of 0·001 per cm. light path per minute of incubation at 25°C; the definition does not mention the volume of serum in which one unit of activity is contained, but from the rest of the article it is apparent that they report units per ml.

(5) Bowers et al.[5] used a similar technique to (2), (3), and (4) but incubated at 37°C and read the extinction at 355 mμ. They professed to use the Karmen units of (2) above, but as the S.G.O.T. activity is increased by raising the temperature of incubation, the unit of Bowers and his colleagues must be different, apart from the effect of using a different wavelength. These authors did not report units per ml. of serum per minute. It must be inferred that their unit is an activity causing a fall in the extinction coefficient of 0·001 per ml. of serum per minute, but this is not explicitly stated.

(6) Cabaud et al.[6] determined S.G.O.T. by catalytical transformation into pyruvate of the oxaloacetate produced by the reaction and determination of the pyruvate by means of its phenylhydrazone. Their unit was an activity in 1 ml. serum which produced 1 μg. pyruvate in 20 minutes at 26°C.

(7) Wróblewski and Cabaud [7] applied the technique of (6) to S.G.P.T. using the same unit.

1. Karmen, A., Wróblewski, F., LaDue, J. S. *J. clin. Invest.* 1955, **34**, 126.
2. Karmen, A. *ibid.* p. 131.
3. Wróblewski, F., LaDue, J. S. *Proc. Soc. exp. Biol., N.Y.* 1956, **91**, 569.
4. Steinberg, D., Baldwin, D., Ostrow, B. H. *J. Lab. clin. Med.* 1956, **48**, 144.
5. Bowers, G. N., Durant, J. R., Beckett, R. S., Tennant, R. *Amer. J. clin. Path.* 1958, **30**, 1.
6. Cabaud, P., Leeper, R., Wróblewski, F. *ibid.* 1956, **26**, 1101.
7. Wróblewski, F., Cabaud, P. *ibid.* 1957, **27**, 235.

(8) Reitman and Frankel [8] simplified the technique of (6). Incubation was at 40°C for 1 hour for S.G.O.T. and for 30 minutes for S.G.P.T. The dinitro-phenylhydrazones were then formed and the change in optical density at 505 mμ determined by comparison with control tubes. For each optical system (colorimeter and filters) a calibration curve had to be prepared, to express this difference as a pyruvate/α-ketoglutarate ratio. A once-for-all determination by Reitman and Frankel relates this pyruvate/α-ketoglutarate ratio to transaminase units, claimed to be those of Karmen, determined by techniques (2) and (3), but adjusted to 25°C by Steinberg's correction (4). It is to be inferred that, subject to the temperature correction, by one transaminase unit Reitman and Frankel mean one Karmen unit per ml. serum per minute. Results obtained by the Reitman and Frankel procedure are usually quoted in "Sigma-Frankel units".

(9) King [9] used a colorimetric technique similar to (8). He defined his unit as that activity in 100 ml. serum which will convert 1 μmol amino-acid to ketoacid in one hour at 37°C.

The normal ranges of these various authors are set out in the accompanying table.

NORMAL VALUE OF SERUM-TRANSAMINASE ACTIVITY IN ADULTS ACCORDING TO VARIOUS AUTHORS

Author	S.G.O.T.			S.G.P.T.		
	No. of normal subjects	Range	Mean	No. of normal subjects	Range	Mean
Karmen, Wróblewski, and LaDue [1]	88	0·41–1·36	0·622	39	0·21–1·01	0·525
Karmen [2]	50	9–32	19·6	..	..	..
Wróblewski and LaDue [3] ..	..	..	..	260	5–35	16
Steinberg et al.[4] ..	20	10–33	16	..	..	..
Baron et al.[10]* ..	25	8–25*	16	..	..	..
Bowers et al.[5] ..	50	16–44†	25	50	6–45	22
Cabaud et al.[6] ..	35	4–40	16·4	..	..	..
Wróblewski and Cabaud [7] ..	..	..	..	50	1–45	22
Reitman and Frankel [8] ..	72	8–40	..	22	5–30	..
King [9]	80	23–107	67·05	35	22–110	54·71

* These authors used Karmen's (1955) spectrophotométric method. The results were corrected by means of a factor to 20°C: their unit is presumably a decrease in the extinction coefficient of 0·001 per ml. serum per minute of incubation at 20°C, although this is not explicitly stated.

† These values were obtained using 0·2 ml. serum. Using 0·5 ml. these authors quote the values 7–29 with mean 18. Inspection of the absorption curves in their paper suggests that this difference may well be due to departures from the Bouguer-Beer law due to optical causes (white-light error).

In view of the confusion in this field, we feel that your statement (Dec. 20, p. 1318) that the normal S.G.O.T. is 10–40 units, and the normal S.G.P.T. is 1–45 units, without specifying the units, is an unfortunate oversimplification.

It seems to us desirable that all laboratories determining S.G.O.T. and S.G.P.T. by measurement of the amount of a reactant produced in a given time should use the same unit; this unit should express the amount of a reactant appearing (or disappearing) as a result of the reaction. Wróblewski [11] has pointed out that the spectrophotometric techniques (2, 3, 4, and 5) measure a different aspect of transaminase activity than do the colorimetric techniques (6, 7, 8, and 9) and the results obtained by the two procedures are not entirely comparable. The Sigma-Frankel unit expresses colorimetric results in spectrophotometric units: this seems to us arbitrary, complicated, unnecessary, and, in the long run, likely to be unsatisfactory.

We suggest that King's unit [9] be used for colorimetric determinations. It expresses the result in terms of reactant formed and can thus be applied to any technique which measures amounts of reactant formed or disappeared, subject to incubation taking place at 37°C. It has the great convenience of providing a normal range which avoids decimals and does not run into the hundreds.

Department of Chemical Pathology, The Royal Hospital, Sheffield.

JOHN DALY
ARTHUR JORDAN.

8. Reitman, S., Frankel, S. *ibid.* 1957, **28**, 56.
9. King, J. *J. med. Lab. Technol.* 1958, **15**, 17.
10. Baron, D. N., Alexander, C. P., Bell, J. L., Oakley, C. M. *Quart. J. Med.* 1958, **27**, 533.
11. Wróblewski, F. *in* Advances in Clinical Chemistry; vol. 1. New York, 1958.

MITRAL INCOMPETENCE

SIR,—In your leading article of Jan. 17 you state that the main problems concern assessment of degree and surgical correction; but it is just as important to learn to diagnose the nature of the defect responsible for regurgitation if the surgeon is not to be presented with irreparable cases.

Mitral incompetence caused by shrinkage of the mural cusp from rheumatic heart-disease may be treated by suturing 'Ivalon' sponge to the mural cusp in such a way as to form a cushion against which a pliant and mobile aortic cusp can close in systole. The operation has been performed by Lillehei et al.[1] and Kay et al.[2] in the U.S.A., and by Wooler,[3] who used a Melrose N.E.P. pump-oxygenator, in this country. Wooler's team consider that mitral incompetence caused by disease of the mural cusp may be diagnosed at the bedside when loud mitral opening and closing snaps are heard in patients with the systolic murmur of mitral regurgitation.[3] In each of twelve patients who presented with these clinical signs, cardotomy revealed a soft and mobile aortic cusp and a shrunken immobile mural cusp. This type of lesion has not been found in patients with mitral regurgitation in the absence of loud snaps.

I agree that operation should be performed before the vicious circle [4] of mitral incompetence has progressed to the stage of gross dilation of the atrioventricular ring and myocardial damage.

Thoracic Department, General Infirmary, Leeds.

PETER NIXON.

1. Lillehei, C. W., Gott, V. L., DeWall, R. A., Varco, R. L. *J. thorac. Surg.* 1958, **35**, 154.
2. Kay, E. B., Nogueira, C., Head, L. R., Coenan, J. P., Zimmerman, H. A. *ibid.* 1958, **36**, 677.
3. Nixon, P. G. F., Wooler, G. H., Radigan, L. R. *Circulation* (in the press).
4. Burchell, H. B., Edwards, J. E. *ibid.* 1953, **7**, 747.

STAPHYLOCOCCAL DISEASE IN HOSPITALS

SIR,—I work in a hospital where for some years the incidence of infection in clean operation wounds has been reviewed monthly by a committee. The operating-theatre ventilation was designed by someone properly briefed and of the highest qualifications for this particular task. I am therefore not deceived about the incidence of wound infection nor complacent, but I confess that I am one of those readers whose boredom you feared—bored by repeated exhortations based, not on the incidence of wound infections, but on the presence of staphylococci. Dr. R. E. O. Williams describes, in last week's issue, the vagaries of staphylococcal infection: he knows of instances when carriers failed to start epidemics, and when epidemics ceased although the carrier continued. Wondering why, he writes: "It might be (and we must hope often is) that aseptic precautions prevent spread even of the dangerous strain from the heavy dispenser."

Of course we must never relax and must intensify our precautions, but if all the exhortations of all the committees are to be implemented in all hospitals, the cost will be enormous, and hope is an inadequate basis for demanding so large an expenditure, which might prove misdirected. Surely it is worth trying a pilot scheme in one or two hospitals while the rest of us do what we can with our existing resources. Let the engineers, matrons, secretaries and administrators, builders, bacteriologists, and laundry-

men make their plans, let the Treasury spend without counting the cost: then, when the dust and staphylococci disturbed by the rebuilding have settled, let surgical teams work for a year and let the results be published. Then we might get some facts about wound infection and staphylococcal infestation.

London, W.1. CECIL FLEMMING.

DANGERS OF "CHEAP" CORTISONE TABLETS

SIR,—Dr. Bush, in his letter last week, suggests that, in view of the shaky biological evidence so far produced concerning the alleged insufficiency of material supplied by this company, further acceptable chemical evidence should be obtained. He goes on to suggest either chromatographic tests or infra-red spectroscopy, or both.

Not only do we agree with this view but in fact we ourselves were doubtful as to the sufficiency of the tests specified in the 1958 edition of the *British Pharmacopœia* and had already decided to have an infra-red spectrogram carried out as suggested by Dr. Bush.

This test has now been completed at the University of London, not only on material extracted (using chloroform) from the batch of tablets referred to in Professor Rosenheim's letter, but also on material extracted from sample tablets manufactured by two of our main competitors.

All three spectra have been found to be virtually identical with one another and with a reference sample of cortisone acetate. Ultraviolet spectra obtained at the same time on alcoholic extracts all showed a single peak at 238 mμ.

The Ministry of Health and Medical Research Council have been informed as to these tests.

Ward Casson Ltd.,
15, Hay Hill, London, W.1. D. O. HOLLAND
Technical director.

GASTRIC HYPERSECRETION

SIR,—We wish to congratulate Dr. Summerskill on his article (Jan. 17), describing a case of Zollinger-Ellison syndrome,[1] in which he speculates on the possible role of glucagon as the ulcerogenic factor. The effect of glucagon on acid gastric secretion has been studied by Robinson et al.[2] in seven subjects, four of whom were known to have peptic ulcer. The dose of glucagon used was 1·5 mg., and diminution in output of hydrochloric acid was observed in each case.

EFFECT OF INTRAVENOUS GLUCAGON 0·01 MG. PER KG. BODY-WEIGHT ON GASTRIC SECRETION IN SIX SUBJECTS

Subject no.	Hydrochloric acid (mEq.)	
	Pre-glucagon hour	Post-glucagon hour
1	6·43	4·60
2	15·25	5·40
3	3·57	1·71
4	5·96	3·20
5	1·97	0·37
6	1·21	0·67

We have noted the effect of intravenous glucagon (0·01 mg. per kg. body-weight) on gastric secretion in six subjects, none of whom had alimentary disease (see accompanying table). Partial inhibition of acid output was recorded in all six. The available evidence does not suggest that glucagon is responsible for the recurrent severe peptic ulceration in this syndrome, although the effect on gastric function of prolonged administration of the hormone has yet to be established.

We are indebted to Messrs. Eli Lilly & Co., Ltd., for supplies of glucagon.

Southern General Hospital,
Glasgow, S.W.1. J. H. C. DALL
A. G. MELROSE.

1. Zollinger, R. M., Ellison, E. H. *Ann. Surg.* 1955, **142**, 709.
2. Robinson, R. M., Harris, K., Hlad, C. J., Eiseman B. *Proc. Soc. exp. Biol., N.Y.* 1957, **96**, 518.

NEW-TYPE OXYGEN CYLINDERS: A WARNING

SIR,—The anæsthetic apparatuses in this hospital have recently been converted to take the new type of non-interchangeable gas cylinders with the American type of valve spindle.

During the course of an anæsthetic an oxygen cylinder became empty, and on attempting to turn on the full cylinder it was found that the new key supplied could not be used owing to a burred spindle. The old-type universal key spanner had been taken away as superfluous, and no oxygen was available until the empty cylinder had been changed. Fortunately the patient was not on controlled respiration, or he might well have died.

Anæsthetists are advised to retain their old universal key spanners and to check all spindle fittings before using the new type of cylinder.

West Suffolk General Hospital,
Bury St. Edmunds. H. MARCUS BIRD.

TESTOSTERONE IN DEFECTIVE SPERMATOGENESIS

SIR,—With regard to Dr. Powell's suggestion (Jan. 24) that we might have made the comment that "fathers are not always husbands", we were not so naïve as his statement would appear to suggest. We thought, however, that such a remark would have been out of place in a scientific paper and preferred to allow our readers to draw their own conclusions, as Dr. Powell has done. On the other hand, his comment surely cannot apply to all 9 patients with sperm counts of 10 million per ml. and less, although undoubtedly it might apply to the patient with azoospermia.

St. Bartholomew's Hospital,
London, E.C.1. A. W. SPENCE
V. C. MEDVEI.

RETICULO-ENDOTHELIAL SYSTEM

SIR,—May I comment on your review last week of my book *The Reticulo-Endothelial System in Growth and Tumour Formation.*

You correctly state that "it is concluded that malignant growths lack functioning macrophages and specific innervation". Later on you also correctly sum up my conclusion that "the absence of macrophage reaction within malignant tumours may explain . . . the loss of bodily control of neoplastic cells". Yet in another sentence you state that "Cancer is regarded as the result of cell mutation with a macrophage reaction to inflammation and trauma". This seems surprising, since I was at pains to point out the exact opposite—namely, that there are no macrophages in malignant tumours, which in cellular growths show no inflammatory response or reparative reaction to trauma. Furthermore, the expression "macrophage reaction to inflammation" is meaningless. Surely this last statement is a typographical error and should read: "Cancer is regarded as the result of cell mutation with an *absence* of macrophage reaction to noxious agents and trauma (within the malignant tissue)."

London, W.1. ROGER WYBURN-MASON.

*** We are grateful to Dr. Wyburn-Mason for this clarification.—ED. L.

WORLD SUPPLY OF UNSATURATED OILS

Mr. D. PURDIE, manager of the professional services department, Armour Pharmaceutical Company, Eastbourne, writes:

Dr. Brown and Dr. Page (Jan. 17) refer to a previous letter by Dr. Bourdillon in which he blamed the Board of Trade import restrictions for depriving special groups of the benefits of corn oil. We wish to point out that there are no restrictions on the importation of safflower oil which, of all the vegetable oils, has the highest content of linoleic acid, an essential fatty acid, and which we use for the production of 'Arcofac', a palatable emulsion for the reduction of serum-cholesterol.

Parliament

Second Reading of the Mental Health Bill

THE welcome which the House of Commons last Monday offered to the principles and purposes of this Bill at its second reading was marred only by the uneasiness which many members clearly felt about its practical implications. Their chief criticism was that local authorities are given permissive (and not mandatory) powers to provide the extended mental health services without which the Bill will remain largely ineffective.

In his opening speech Mr. DEREK WALKER-SMITH, the Minister of Health, said that the Bill [1] followed closely the recommendations of the Royal Commission, and in some respects improved on them. Under the Bill, the small element of compulsion which was retained was hedged by additional safeguards for the patient. Two medical recommendations would be needed (except in an emergency when one would suffice for the first seventy-two hours). Patients would be able to apply to a mental health review tribunal at any time within the first six months after admission. Broadly speaking the power of discharge would now be held by the doctor in charge of the patient's treatment, by the managers of the hospital or nursing-home, by the patient's nearest relative, and, on application, by a tribunal.

Turning to the provisions for psychopaths and subnormals he said that these people were only liable to compulsory admission under the age of 21 (that is, during their formative years when they were most accessible to treatment and training). Ordinarily they would be entitled to discharge at 25. As a safeguard for the public they would be examined by the "responsible medical officer" at the age of 25, and if he thought them unfit for release they could be detained in hospital; but they would have the right of appeal.

One of the main principles which the Bill sought to pursue was the reorientation of the mental health service away from institutional care towards care in the community. Hospitals and local authorities both had their part to play, and so had the public. The idea of caring for the mentally disordered in the community was still often accepted only as a principle. Too often it became a different matter if a hostel was to be provided in the house next door or even in the same neighbourhood.

The local authorities had a wide range of services, and their contribution to community care did not, in fact, depend on new legislation. In recent years their mental health services had been steadily expanding, as was shown by the progressive increase in their expenditure which had risen from £2,300,000 in 1954–55 to £3,600,000 in 1957–58; for 1958–59 it was estimated at £4 million. A generous allowance in the next two-year period for expenditure on the mental-health services had been made in arriving at the total of the general grant. Mr. Walker-Smith admitted that the Royal Commission had recommended that there should be a specific grant, or other special Exchequer assistance, for capital development by local authorities; but this recommendation had been made against the pre-general-grant background. The expansion of local-authority capital expenditure was also substantial; the value of work authorised in 1958 was more than double that authorised in 1956. The local health authorities' powers could be converted into duties at any time by the Minister's direction. But the conversion of a power into a duty did not automatically call the services into being, since logistical factors were the limiting factors. When the time came, consideration would be given to converting some, or all, of these powers into duties. Direction might have to be used, but he himself preferred voluntary to directed effort.

Dr. EDITH SUMMERSKILL believed that the success of the Bill would be determined by our ability to find the manpower and the finance, and to educate the public. There were only 500 psychiatric social workers in the whole of the country. The shortage of psychiatrists was largely due to the failure to teach psychiatry adequately in the medical schools, and to the prejudice of the medical profession itself. Yet 45% of the hospital beds in this country were occupied by patients with some form of mental disturbance.

If some local authorities failed to provide for the mentally sick, as they had failed to provide for the aged under permissive legislation, this Bill might well prove abortive. She was also uneasy about the psychopathic group. The right of the hospital to refuse admission to a patient might bear heavily on them. Some kind of machinery might be needed to regulate admission.

Mr. CHRISTOPHER MAYHEW feared that there was danger of overestimating the benefits from the mere passage of the Bill. A great deal would depend on how the local authorities rose to the occasion; in the past, and in general, their efforts had been disappointing. His anxiety was not relieved by the figures quoted by the Minister. £4 million seemed totally inadequate.

Again, the impact of the emergence of thousands of patients into the community from hospitals might be a good thing, but it might create difficulty as well. When the patient and ex-patient came into closer contact with the community, that would probably increase understanding. But it would also increase the need for patience and generosity on the part of the community. It would be wrong to think that the difficulties of accepting patients and ex-patients into the community were due simply to ignorance or prejudice. By the very nature of their handicap, mentally ill and mentally deficient people were particularly hard to integrate into the community.

Dr. A. D. D. BROUGHTON thought that the Bill was still ahead of the present views of many people, and that many local authorities had little idea what their duties would amount to. He was not happy that the patient could be detained for longer periods on two medical certificates. When a patient was compulsorily detained, he was losing important civil rights. Dr. Broughton thought that a doctor was not qualified to deprive a person of civil rights. The responsibility would be better left with justices of the peace.

Mr. KENNETH ROBINSON said that local authorities which had been providing reasonable community care would do better in the future; but the very much larger number of authorities which had made little or no provision for mental-health services would continue to do nothing, for they had had permissive powers for a long time and had taken no advantage of them. He suggested that we should give two years' notice, during which period schemes must be prepared and submitted to the Minister for approval. Finance would have to be provided from central Government funds.

One of the corollaries of the Bill was that experimental units for the treatment of psychopaths should be set up. Because mental hospitals were now dedesignated they had the right to refuse a patient. That might lead to difficulties especially for the unwanted type of patient, including the psychopath. Some obligation had to be placed somewhere, and the regional hospital boards seemed the right bodies to shoulder that responsibility.

Dr. REGINALD BENNETT wondered whether the pursuit of freedom from restriction and compulsion was not leaping ahead of public opinion. Would doctors now be able to persuade people who needed treatment to enter hospital? He, too, was dissatisfied with the elimination of the justice of the peace as the committing authority. The continued holding of a patient in hospital was a custodial matter, and should not

1. See *Lancet*, Jan. 10, 1959, p. 94.

be a matter for the doctor's certificate. Could the mental health review tribunals in some way be given this duty? We must have some new sort of institution for psychopaths.

Dr. DONALD JOHNSON was still uneasy about the safeguards in cases of compulsory detention, and he too suggested that the mental health review tribunals should replace the justice of the peace in admission and detention procedure.

Mrs. E. M. BRADDOCK (who was a member of the Commission) said that under the terms of the Bill progressive authorities would expand and add to their mental-health services (especially for the training and accommodation of mental defectives); but in scattered areas and country areas local authorities that were not so progressive or compact simply would not bother unless there was some form of compulsion and financial help.

Mr. RICHARD FORT pointed out that, though the increase in consultant posts sounded splendid percentagewise—52% over ten years—there were in fact still only 615 consultant psychiatrists in the country. Senior-registrar posts had been increased from 113 to 144, but unfortunately only 117 of those had been filled. When we talked about medical certification, it was worth remembering that most of those who would have to undertake this work would have had no more training for it than most Members of the House.

Mr. ARTHUR BLENKINSOP saw in the emphasis on the need for more community care an opportunity to bring together the three parts of the National Health Service. It would be a disaster if this hopeful new enterprise were put in a straitjacket by means of the block grant. £4 million for the mental health services of all local authorities was totally inadequate.

Sir HARRY HYLTON-FOSTER, the Solicitor-General, in the course of his reply dealt with the problem of whether the local-authority provisions in the Bill should be made mandatory. The Minister, he pointed out, could at any time impose a duty under the Bill. All the local health authorities in the country had submitted their schemes, and the Minister proposed by circular to ask them to review all their arrangements and, if necessary, amend their proposals. With the present shortage of staff the brake on expansion was not so much finance as staff. There were only about 600 full-time mental welfare officers; of those, 200 did not do the duties of the duly authorised officer. Psychiatric social workers were also very scarce.

It was the intention of the Minister that regional hospital boards should ensure that a patient urgently requiring psychiatric treatment should be admitted to the hospital best able to give him that treatment. Arrangements for this could suitably vary from region to region.

QUESTION TIME

Prescription Charges

Mr. ARTHUR BLENKINSOP asked the Minister of Health what proposals he had for introducing amending legislation to enable patients who choose private medical treatment to have the cost of prescriptions charged against the National Health Service.—Mr. DEREK WALKER-SMITH replied: None at the moment; but the British Medical Association have asked for an early discussion on this matter and I shall, of course, give careful consideration to what they say. Mr. BLENKINSOP: Will the Minister give an assurance that there will be no suggestion of trying to introduce what amounts to levels and standards of service in the National Health Service? This would be damaging and would destroy the whole meaning of the National Health Service itself.—Mr. WALKER-SMITH: I think the hon. Gentleman put the supplementary question in such general terms as not to be capable of a precise answer. What I would say is that in considering the advice that I receive from the British Medical Association I shall, of course, bear the matter in mind in the context of the whole public interest.

Mr. R. E. PRENTICE asked the Minister whether he was aware that the system of charging 1*s.* for each item on a doctor's prescription had led to an increase in the cost of the prescription service, owing to the tendency of the doctors to prescribe larger quantities in order to reduce the burden on poorer patients; and whether he would consider the abolition of these charges.—Mr. WALKER-SMITH: These charges are being continued at present. I, of course, always keep under consideration all relevant circumstances relating to the financing of the National Health Service. In this context the additional cost due to the prescribing of larger quantities for chronic conditions must be set against the saving resulting from the substantial reduction in the number of prescriptions and the additional receipts from charges. I am satisfied that, as a result of the change in the basis of patients' charges, the burden on the Exchequer was less than it would otherwise have been.

Mr. BLENKINSOP: Is the Minister not now convinced after the report published in *The Lancet*,[1] that this new charge is, in fact, a waste and medically it can be dangerous?—Mr. WALKER-SMITH: What the article in *The Lancet* shows is that the drug bill for 1957 was larger than the drug bill for 1956. But that is not the material question. The material question is whether the drug bill for 1957 was as large as it would have been had we continued the old basis, and it is on that that I say a saving has been made. Mr. PRENTICE: Did not the Minister see that the statistical analysis in *The Lancet* indicated that something like 40% of the increase in the average prescription was due to the tendency of doctors to prescribe larger quantities because they wanted to avoid putting on to their poorer patients a higher bill? Does not this show that the whole policy was misconceived?—Mr. WALKER-SMITH: No, I do not think so. It is appropriate for doctors to prescribe large quantities in chronic cases, and that is not necessarily a wasteful procedure. To meet cases of hardship there is, of course, a system of refund in connection with the National Assistance Board.

Obituary

ZEBULON MENNELL

M.B. Lond., F.F.A. R.C.S., D.A.

Dr. Z. Mennell, consulting anæsthetist to St. Thomas's Hospital, died on Jan. 20 at the age of 82.

He was born in London, the son of another Dr. Zebulon Mennell, and he was educated at St. Paul's School. He qualified from St. Thomas's Hospital in 1900, and after holding house-appointments and clinical assistantships there he started in general practice in the West End of London in 1902. As a student he had been greatly interested in anæsthetics, and when his old teacher Walter Tyrrell retired in 1904 Mennell joined the anæsthetic team at St. Thomas's. But until he retired he kept on his general practice, for he held that it gave him a balanced approach to anæsthesia.

St. Thomas's Hospital Gazette

Later he was also appointed to the staff of the National Hospital, Queen Square, where he worked with Victor Horsley and Percy Sargent. But St. Thomas's was his chief interest, and for over forty years remained the centre of his professional life.

Despite a busy private practice until he retired in 1936, after having been senior anæsthetist for fifteen years, he always spent at least three days a week at St. Thomas's. He was also lecturer in anæsthetics; and when he retired one of his students wrote:

> "As a teacher he is well known as the supreme master of ether. Most of us have memories of his wizardry with Clover's apparatus: of how easy he made induction seem, and of how difficult we found it at first when his guiding hand was removed. We remember the relief with which we

1. Martin, J. P., Williams S. *Lancet*, Jan. 3. 1959, p. 36.

connected our patient to the Mennell bottle and were free to listen to an exposition of our former difficulties and instruction for their future avoidance. We remember how his calm presence would quiet a nervous patient, and give assurance to an often equally nervous anæsthetic clerk."

During the late war he returned to help at St. Thomas's in London, and later at the hospital at Hydestile. When he retired from the National Hospital in 1945 he was appointed the hospital's first consulting anæsthetist.

Because of his appointment at the National Hospital one of his chief interests was naturally anæsthesia for intracranial surgery, and before the 1914–18 war he was a pioneer in the use of hedonal and later in the administration of ether by intratracheal insufflation. When slower techniques of operation were introduced he abandoned this procedure for endotracheal inhalation of nitrous oxide and oxygen, with minimal reinforcement by ether or chloroform. But neither his skill nor his work was limited to this narrow fold. He was adept in the use of the laryngoscope and at securing abdominal relaxation by means of deep ether anæsthesia. He was elected a fellow of the new Faculty of Anæsthetists in 1948, and he was a Snow medallist and an Embley lecturer.

J. F. R. writes:

"Zeb Mennell was first and foremost a fine anæsthetist, confident and always unruffled. His reputation grew rapidly and he built up a highly successful anæsthetic practice. His services were in great demand, not only by his hospital colleagues, but by many others who appreciated the quality of his work. It is remarkable that he was also able to find time to carry on a flourishing West End general practice, which he kept on until he retired.

"He had a strong personality and was a man to be reckoned with. He saw the way clear ahead, and achieved his aims with drive and tenacity. At Thomas's, where I knew him as senior anæsthetist for many years, he ran his department firmly and efficiently. But he was always very approachable and gave much help and valuable advice to many a young anæsthetist. Old Thomas's men who were his students will remember with gratitude his excellent practical instruction, and how he always made a point of teaching them how to obtain good abdominal relaxation with ether. This was specially appreciated by those who went into general practice and gave their own anæsthetics. Undoubtedly the happiest and most rewarding part of his career was his long association with Sargent. This gave him a great opportunity to improve methods of anæsthesia for neurosurgery, and it was probably in this field that he made his greatest contribution to the advancement of his specialty."

His wife died in 1951, and he leaves three daughters.

PHILIP GEOFFREY DOYNE

B.A., B.M. Oxon., F.R.C.S.

Mr. Philip Doyne, consulting ophthalmic surgeon to St. Thomas's Hospital and consulting surgeon to the Royal London Ophthalmic Hospital, died at his home at Henley-on-Thames on Jan. 22, at the age of 72.

He was the son of Robert Doyne, founder of the Oxford Eye Hospital and the first master of the Oxford Ophthalmological Congress—an office which was later also held by Philip Doyne. From Winchester he went to Trinity College, Oxford, and to St. Thomas's Hospital, qualifying in 1913. Among the resident posts which he held was that of ophthalmic house-surgeon at St. Thomas's. His first hospital appointment was to the East London Children's Hospital; his interest in children's work continued, and he later became eye surgeon to The Hospital for Sick Children, Great Ormond Street.

During the 1914–18 war he served with the R.A.M.C. in the Mesopotamian campaign. He ended his Army service as an ophthalmic specialist, and he continued this work on his return to civil life. He was appointed assistant surgeon at Moorfields Eye Hospital (as it was then called) in 1922 and ophthalmic surgeon at St. Thomas's two years later.

M. H. W. writes:

"Philip Doyne was a delightful colleague, naturally modest and even a little retiring—his contributions to discussions at medical committees were not very frequent, but when they came they were definite and full of wisdom. He bore his full share of clinical work and teaching, and during the last war he gave all his energies to the maintenance of the ophthalmic service in the St. Thomas's Hospital sector. It was after the end of the war that he was elected master of the Oxford Ophthalmological Congress, and he occupied this position with a distinction which would have gratified his father.

He was amateur foils champion of Great Britain in 1912 and again in 1920, and he went to the United States about that time to represent Great Britain in a fencing team. Though the match was fought the day after they landed, they were only narrowly beaten. He took part in the American championship and achieved second place. He was renowned for his classical style and, though he took part in épée competitions as a member of a team, the foil was the weapon that he preferred and with which he gained his greatest successes. It was difficult to get him to talk of his fencing honours, for it was natural for him to be modest and almost shy about any personal achievement, and this was characteristic of his professional side also."

Mr. Doyne leaves a widow and a daughter.

HUBERT HENRY FOURACRE BARNS

M.B. Lond., F.R.C.S., F.R.C.O.G.

Mr. H. H. Fouracre Barns, who died on Jan. 21 at the age of 48, had been gynæcological surgeon to the Women's Hospital, Soho Square, since 1947; and he had also made his mark by experimental work at University College Hospital.

He qualified in 1936 from U.C.H., where he subsequently held several junior appointments. In 1939 he took the F.R.C.S. and three years later the M.R.C.O.G. In the 1939-45 war he served with the Royal Air Force as a surgical and gynæcological specialist. After the war he was for a time chief assistant in the department of obstetrics and gynæcology at St. Thomas's Hospital; but thereafter he resumed his association with U.C.H. as chief assistant to the obstetric unit. In 1953 he was elected F.R.C.O.G.

G. Q. writes:

"At University College Hospital Fouracre Barns' special knowledge of infertility and pregnancy diabetes made him a valued colleague. He had a wide general surgical training; and this, together with a clear logical mind and natural practical dexterity, soon established him in the front rank of his specialty as clinician, operator, and teacher. Sparing no effort in carrying out his everyday duties, he showed, in addition, a real interest in research and carried out a considerable amount of experimental work, resulting in valuable contributions to the problems of infertility and of pregnancy in diabetes. He had original and constructive ideas on these subjects, and he was painstaking and thorough in his research. He was versatile and inventive, and, being troubled with a painful spine for some years, he developed an ingenious method of operating in the sitting position using a lateral tilt to the operating-table."

Of his work at Soho Square, I. H. writes:

"This hospital, like several others to which he was appointed, soon realised the strength of his personality and how he strived to extend the teaching and research facilities in the hospital. He was instrumental in getting a fertility clinic started, which he supervised and ran with great zeal, and his work in this important sphere of gynæcology has been interrupted at a point when many interesting results must have been forthcoming. He was well known to everyone throughout the world who specialised in work on infertility.

"He instituted the hospital's medical society, and many interesting evening discussions on various aspects of obstetrics and gynæcology resulted from his untiring efforts as its honorary secretary. After each meeting he organised a dinner party held in a local restaurant. Many ex-residents, most of whom have now attained posts of eminence in this specialty, came to these happy meetings.

"On Saturday mornings he could be found taking a tutorial class in pathology at the hospital. This proved very popular with the students. He was a forceful teacher, and his method of imparting knowledge coupled with wise counsel must have brought happy results to many at examination time."

Mr. Fouracre Barns is survived by his wife and a son.

VERNON KENT DRENNAN

M.Ch. Orth. Lpool, F.R.C.S.E.

Mr. Vernon Drennan died on Dec. 19, at the age of 47, in Liverpool, where he had spent his early life.

He graduated M.B. at the university in 1935, and after holding a house-surgeon's post at the Liverpool Stanley Hospital, he took up surgical work at Walton Hospital. In the summer of 1939 he joined the Territorial Army; and in the 1939–45 war he saw much active service, mainly in Burma where he worked as a forward surgeon with the 14th Army.

After returning to Liverpool he gained the F.R.C.S.E. in 1948 and graduated M.CH. ORTH. in 1950. The following year he was appointed consultant orthopædic and traumatic surgeon to the Clwyd and Deeside hospital area. In the post-war years he continued to serve in the Territorial Army, and commanded the 8th Liverpool General Hospital.

C. T. A. B. writes:

"At Walton Hospital Vernon Drennan came under the inspiring influence of the late Walter Diggle, by whom his interest in surgery was both stimulated and developed. Here too qualities of sound common sense and good clinical judgment matured. In his appointment to the Clwyd and Deeside hospital area he found full opportunity to exercise his skill; and he built up a large practice, to which he gave his energy and time unsparingly. The last three years of his life were spent with the knowledge that his time was short; but he never allowed this to interfere with his work, and despite increasing physical discomfort he continued to work until shortly before his death. Outside his professional work he was a great lover of music and the keenest of anglers: nothing gave him greater pleasure than a few hours' fishing on the Clwyd."

F. E. D. G. adds:

"It was as a T.A. officer that I knew Vernon Drennan best. I knew him as a major, a lieut.-colonel, and a colonel. Whatever his rank he never changed, and he made a first-class commanding officer. Somehow he never seemed to issue orders—he expressed a wish and it was a point of honour with all ranks that the wish was fulfilled. With the men he was wise, just, and a true friend. Laughter was never far from his lips and always in his eyes, and he faced his final illness with a courage that inspired his friends and fellow officers."

Mr. Drennan is survived by his wife and two children.

GEORGE CHESNEY

O.B.E., M.D. Belf., D.P.H.

Dr. Chesney, formerly medical officer of health for Poole, died on Jan. 16 at the age of 64.

He was born at Ballymena, Co. Antrim, and educated at the Ballymena Academy and Queen's University, Belfast, where he qualified in 1916. During the 1914–18 war he served in India, Burma, Mesopotamia, and Persia with the R.A.M.C. Later he returned to Belfast as assistant in hygiene and bacteriology to Prof. W. J. Willson at Queen's University, and in 1920 he took the D.P.H. After travel in the Far East and a year as acting bacteriologist in the department of pathology of the University of Saskatchewan, he spent seven years in general practice in Manchester.

He began his career in public health in 1929 when he was appointed deputy medical officer of health for Poole. In 1939 he was recalled to the R.A.M.C. in which he served as D.A.D.H., Southern Command, until 1942 when, on the retirement of Dr. R. J. Maule Horne, he was appointed medical officer of health for Poole. During his service in Poole he was medical superintendent of the Alderney (Infectious Diseases) Hospital and he was appointed a consultant in infectious diseases.

Owing to ill health he had to retire from his appointment as medical officer of health in 1952, but he continued his work as consultant until 1957. In 1953 he was appointed O.B.E. for his work in diphtheria immunisation.

A colleague writes:

"Dr. Chesney gained international recognition for his work on diphtheria immunisation, and in 1936 he read a paper on this subject before the International Congress on Microbiology. His untiring efforts and ultimate success in solving the problem of the widespread Bournemouth, Poole, and Christchurch typhoid outbreak in 1936 were highly commended. When Poole was the only civil marine airport in the country he introduced a revised system to prevent the importation of infectious disease from abroad. A year later the merit of this procedure was clearly recognised by its international adoption."

REGINALD STEPHEN TOWNSEND

M.C., M.D. Lond., M.R.C.O.G.

Colonel Townsend, who died on Jan. 17 after a long illness, had a distinguished career in the Indian Medical Service.

After qualifying from St. Bartholomew's Hospital in 1907 he entered the I.M.S. During the 1914–18 war he served in East Africa with distinction, and was awarded the M.C. for his gallantry in the field. Between the wars he entered civil employment in the United Provinces, where he held many of the most important surgeoncies. On reaching administrative rank he was posted to the North West Province as inspector-general of civil hospitals. He retired shortly before the late war, in which he did trooping service as senior medical officer. He also served for some years with the Ministry of Pensions as an examining medical officer.

A colleague writes:

"Colonel Townsend's latter years were dogged by ill health, and he lived in retirement, but he will be remembered with affection by many of his former colleagues and patients in the United Provinces."

Appointments

COHEN, S. J., M.B. W'srand, F.R.C.S., M.R.C.P.E.: assistant surgeon, The Hospital for Sick Children, Great Ormond Street, London.

FOUNTAIN, J. R., M.D. Edin., M.R.C.P.E.: part-time consultant in general medicine and geriatrics, Bingley, Keighley, Skipton, and Settle areas, Yorkshire.

HOULT, J. G., M.B. Birm., D.C.H., D.PATH.: consultant pathologist, Birmingham (Dudley Road) group of hospitals.

MATHERS, J. R., M.B. St. And., D.P.M.: consultant psychiatrist and medical superintendent, Rubery Hill Hospital, Birmingham.

MUNRO, D. E., M.D. Glasg., D.P.M.: consultant in psychiatry, Clifton Hospital, Yorkshire.

REID, J. J. A., T.D., M.B., B.SC. St. And., D.P.H.: deputy M.O. and deputy principal school M.O., Northamptonshire.

VANIER, THERESE M., M.B. Cantab.: medical registrar, The Hospital for Sick Children, Great Ormond Street, London.

East Anglian Regional Hospital Board:

GAIND, RAGHUNANDAN, M.B. Punjab, F.R.F.P.S.: medical registrar, West Norfolk and King's Lynn General Hospital.

GUPTA, P. B., M.B. Bombay, M.CH. ORTH., F.R.C.S.E. Lpool: orthopædic registrar, Norfolk and Norwich Hospital.

HUNTER, J. L., M.B. Edin.: anæsthetic registrar, West Norfolk and King's Lynn General Hospital.

KAPUR, Y. P., M.B. Punjab, D.L.O.: E.N.T. registrar, Norfolk and Norwich Hospital and Jenny Lind Children's Hospital.

SHRIKHANDE, U. N., M.B. Bombay: surgical registrar, County Hospital, Doddington.

STOUT, R. J., M.B. Lond., F.F.A. R.C.S., D.A.: consultant anæsthetist, North Cambridgeshire Hospital group.

UTHAPPA, P. C., M.B. Madras: surgical registrar, North Cambridgeshire Hospital, Wisbech.

Notes and News

W.H.O. EXECUTIVE BOARD

WHEN the 23rd session of the W.H.O. Executive Board opened in Geneva on Jan. 20, Dr. M. G. Candau, director-general of the Organisation, reported that the world-wide malaria-eradication campaign was threatened by shortage of funds. Available funds fell short by about $1·3 million of the amount needed for malaria eradication in 1959. Fund-raising activities, undertaken at the request of the World Health Assembly, had failed. Except for the $8 million contribution of the United States,[1] most of the economically developed countries had not responded to appeals; a few of them had made very modest contributions. It was an unsound situation for the World Malaria Fund (which had received $8,443,300) to depend almost entirely on the support of one single country. The Executive Board and the World Health Assembly would have to give urgent attention to this problem. "We have had good-will, nice words, and no money," Dr. Candau concluded. This "plain, blunt, and very necessary statement" was welcomed by Dr. P. E. Moore (Canada), the chairman.

Earlier Dr. P. M. Kaul, assistant director-general, had described progress in the malaria-eradication campaign on all continents.

In *southern Africa* the results of residual-insecticide spraying were encouraging. It was now time for W.H.O. to sponsor a large interterritorial malaria-eradication project in the south-east corner of the continent. Despite successes in the Southern Cameroons, difficulties were being experienced in *tropical Africa*, and pilot projects to find out the best means of interrupting transmission were recognised as the best way to solve the technical problems. The costs in Africa would be high; but, despite difficulties, eradication must remain the goal.

In *the Americas* the picture was more cheerful; and eradication programmes, planned or in operation, included all countries and territories except Cuba, British Guiana, and Dominica. Dominica was hastening to complete a plan for total coverage; British Guiana had succeeded in eradicating the disease except in the jungle interior, which was thinly populated. In general the prospects of achieving total success were very bright.

In the *Eastern Mediterranean* eradication programmes were now being implemented in Iraq, Iran, Israel, Jordan, Lebanon, and the United Arab Republic (Syrian Province). Other countries which had carried on control programmes for some years were fast approaching the pre-eradication stage.

In the *European region*, of the 13 countries with indigenous malaria 10 now had operating programmes covering the entire country; (Algeria) had none as yet, another (Morocco) hoped to achieve total coverage by 1961.

In the *South-East Asia region* malaria had existed until recent years in all countries, but had been eliminated from certain parts of India, Ceylon, and Thailand. Nearly all governments had accepted the principle of eradication.

In the *Western Pacific region* there were gaps in knowledge. It was known, however, that anopheline mosquitoes, and therefore malaria, were absent from 1 country and 18 territories out of the 14 countries and 34 territories of this region. Japan seemed to be approaching eradication; China (Taiwan), the Philippines, Sarawak, and Cambodia were progressing in that direction; and plans were being made in other countries.

According to Dr. Kaul, if the funds necessary to continue this cooperative effort were not provided, programmes in some countries would collapse and the money already spent would be wasted. "This, and the threat of resistance of the mosquito carrier of malaria to insecticides," he said, "are the two most powerful arguments against delay or slowing down of our hard-fought global campaign."

The Board appointed Dr. Abraham Horwitz (Chile) as director of the W.H.O. regional office for the Americas (Pan American Sanitary Bureau) in succession to Dr. Fred L. Soper; and it extended for a further five years the appointment of Dr. F. J. C. Cambournac as regional director for Africa.

The Board's report will be submitted to the twelfth World Health Assembly, which will meet in Geneva on May 12.

1. See *Lancet*, Jan. 24, 1959, p. 212.

COURSE IN MEDICAL ADMINISTRATION

THE university department of public health in the London School of Hygiene and Tropical Medicine is to hold, from Feb. 2, a nine-week course in medical administration for administrative medical officers of regional hospital boards. This pilot venture may provide a pattern for courses concerned with other aspects of medical administration. The course consists of six main sections which are interrelated and blended together. They are as follows:

1. That dealing with business administration, which will be provided by the Department of Scientific and Industrial Research and by experts drawn from Ashridge College and from industrial firms.

2. That dealing with central administration of the health services. This section is provided by arrangement with members of the medical staff of the Ministry of Health.

3. That provided by the regional hospital boards' officers themselves. This section will in the main take the form of discussions and of visits to hospitals.

4. That related to the teaching and voluntary hospitals in London and in the Provinces.

5. That contributed by the university departments of public health, medical statistics and epidemiology, applied physiology, occupational health, and psychological medicine.

6. That afforded through other organisations, departments, societies, &c.

FORGED PRESCRIPTIONS

LAST September London Executive Council drew the Minister of Health's attention to a disquieting increase in the number of cases of falsification or forgery of E.C.10 forms, and asked him to consider measures to limit these cases. The Ministry replied in November that the situation was being considered, and it asked that meanwhile further cases should be brought to its notice and that where an Exchequer loss was incurred full details should be supplied, so that the Minister's approval to "write off" the amount lost through fraud could be obtained. At its meeting on Jan. 22 the Council reported three recent prosecutions where prescription forms had been irregularly used to obtain 'Drinamyl' tablets, paraldehyde and 'Nembutal', and dexamphetamine-sulphate tablets. The Council expressed disappointment at the Ministry's reply, for its chief concern was not administrative procedures for "writing off" small sums but the increase in the practice of obtaining drugs by false pretences. The Council have sent to the Minister a further letter asking for early action.

A JOURNAL RENAMED

THE title of the *British Journal of Tuberculosis and Diseases of the Chest* has been changed to the *British Journal of Diseases of the Chest*, and the interests of the journal are widened correspondingly. The January issue of the journal, which is edited by Dr. Philip Ellman and published by Messrs. Baillière, Tindall & Cox,[1] contains greetings from Sir John Charles, Prof. Robert Platt, P.R.C.P., Sir Robert Young, and Sir Clement Price Thomas. The articles include contributions from workers in Australia, Kenya, the West Indies, and the U.S.A.

PUBLIC HEALTH LABORATORY SERVICE

The third edition of "Notes for the Guidance of Medical Officers and General Practitioners" is published in the January, 1959, issue of the *Monthly Bulletin of the Ministry of Health and Public Health Laboratory Service*. The Notes are intended to help practitioners to make the best use of an up-to-date bacteriological laboratory.

Among other things, they include information on the type of specimen required for the laboratory diagnosis of the commoner diseases caused by bacteria and viruses. There is a four-page summary in tabular form which may be found particularly useful. Reprints of the whole article, and of the tabulated summary alone, will be available towards the end of February; either may be obtained, on request, from the nearest laboratory of the P.H.L.S., or from the Director, Public Health Laboratory Service, Medical Research Council, 38, Old Queen Street, London, S.W.1.

1. 7, Henrietta Street, London, W.C.2. Annual subscription 60*s*.; single copies 18*s*.

University of Birmingham

The following degrees have been conferred:

M.D.—D. F. Davies.
Ch.M.—P. G. Bevan.
Ph.D. (in the faculty of medicine).—F. N. Garratt, J. F. Nunn.
M.B., B.Ch.—B. H. Ackers, John Ashton, R. M. Badminton, P. W. Burton, J. S. Coles, C. D. Dalby, J. T. Dennis, D. C. Dukes, Anthony Dunnill, E. E. Genever, D. A. Gibson, Brian Henley, G. R. Horton, Danuta Kaczmarska, J. S. Levett, K. E. Luckman, Shirley M. Machin, R. F. Norris, T. J. Pearman, G. C. Rowe, A. J. R. Smout, G. B. Wolloff.

The university has accepted the offer of the Medical Research Council to establish a neuropharmacology research group in the department of experimental psychiatry under the honorary direction of Dr. P. B. Bradley, senior lecturer in electrophysiology and acting head of the department, for five years in the first instance from August, 1958.

University of Glasgow

Dr. C. M. Fleming has been appointed reader in administrative medicine. The faculty of medicine have intimated to the court their intention to appoint Dr. Fleming as dean in succession to the late Prof. G. M. Wishart.

Dr. Fleming, who qualified from the University of Glasgow in 1929, is at present a principal medical officer in the Department of Health for Scotland, and he has taken a particular interest in postgraduate teaching and the family doctor service organised by the University of Edinburgh.

Royal College of Surgeons of England

On Monday, Feb. 16, at 4 P.M. at the college, Lincoln's Inn Fields, London, W.C.2, Sir Reginald Watson-Jones will give the Hunterian oration. His subject will be Surgery is Destined to the Practice of Medicine.

University of London

The title of professor of physiology in the university ha been conferred on Dr. J. A. B. Gray in respect of his post a University College.

University of Edinburgh

The status of honorary lecturer in periodontology has bee conferred on Mr. J. W. Galloway, L.R.C.P.E., chief dent officer to the Department of Health for Scotland. Dr. D. S Cownie, Dr. A. C. McLaren, and Dr. I. H. Stokoe have bee appointed part-time lecturers in the general-practice teachin unit, and Dr. I. I. Smith and Dr. J. W. Black lecturers in th department of pathology.

Swiney Prize

The Swiney prize, which is given for the best publishe work on medical jurisprudence, has been awarded to Dr. Keit Simpson for the third edition of his book *Forensic Medicin* The award was made by a joint committee of the Royal Societ of Arts and the Royal College of Physicians of London.

On Sunday, Feb. 1, a symposium for general practitioners will b held at the radiotherapeutic centre, Addenbrooke's Hospital, Cam bridge. A symposium on general medical practice will be held at th department of human ecology, Fenner's, Gresham Road, Cambridge on Saturday, Feb. 14. Further particulars may be had from th secretary, medical school, Tennis Court Road, Cambridge.

The Northern Home Counties faculty of the College of Genera Practitioners will hold a meeting on Tuesday, Feb. 10, at 8.30 P.M. a the King's Head Hotel, Harrow-on-the-Hill, Middlesex. Mr. P. D Campbell Jackson will speak on domiciliary obstetric emergencies.

Diary of the Week

FEB. 1 TO 7

Monday, 2nd

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
4 P.M. Dr. Alick Bearn (New York): Biochemical Genetics in Clinical Medicine.
GUY'S HOSPITAL S.E.1
5.15 P.M. Dr. K. S. MacLean: Cortisone.

Tuesday, 3rd

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Dr. A. R. Southwood (Adelaide): Aspects of Preventive Cardiology—1. Elaboration of Public Health. (First of two Milroy lectures.)
ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. Rodney Smith: Anatomy and Physiology of the Bile and Pancreatic Ducts and their Surgical Significance. (Arris and Gale lecture.)
UNIVERSITY OF LONDON
5.30 P.M. (University College, Gower Street, W.C.1.) Prof. G. W. Beadle (U.S.A.): Mendelian Inheritance. (Last of two lectures.)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Pathology.* Prof. R. J. V. Pulvertaft: Cellular Associations in Normal and Abnormal Lymphocytes. (Presidential address.)
8.30 P.M. *Orthopædics.* Mr. J. S. Batchelor: Surgery of the Hip. (Presidential address.)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. O. M. Wrong: Sodium Excretion and the Control of Extracellular Fluid Volume.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Prof. C. Scott Russell: Some Problems of Puberty.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. P. D. Samman: Diseases of the Nails. (First of two lectures.)
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology Department, Dundee.) Prof. Adam Patrick: The Development of Ideas on Some Nervous Diseases—Meningitis. (Last of two lectures.)

Wednesday, 4th

ROYAL SOCIETY OF MEDICINE
5.15 P.M. *History of Medicine.* Prof. A. Leslie Banks: Strafford—The Medical Background.
8 P.M. *Surgery.* Mr. R. V. Cooke: Craftsmanship. (Presidential address.)
POSTGRADUATE MEDICAL SCHOOL
2 P.M. Dr. F. E. Camps: Postmortem Investigation and Interpretation of Head Injuries.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Prof. T. B. Fitzpatrick: Increased (Brown and Grey-Blue) Pigmentation.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. Howard Nicholson: Early Diagnosis of Lung Cancer.
ASSURANCE MEDICAL SOCIETY
5 P.M. (11, Chandos Street, W.1.) Dr. Donald Norris: The Widening Horizon in Medical Insurance. (Presidential address.)
OXFORD UNIVERSITY
5 P.M. (Radcliffe Infirmary.) Prof. L. N. Pyrah: Aspects of Renal Calculus Formation. (Litchfield lecture.)
MIDLAND MEDICAL SOCIETY
8.15 P.M. (36, Harborne Road, Edgbaston, Birmingham, 15.) Mr. L. D. Abrams, Mr. Frank Ashton, Dr. W. A. Hudson: Experiences in the Use of the Extra-Corporeal Heart.
MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School, University of Manchester.) *Medicine.* Dr. C. S. D Don: Treatment of Diabetes. (Presidential address.)
MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (18, Nicolson Street, Edinburgh.) Mr. K. Paterson-Brow Dr. A. G. MacGregor: Thyrotoxicosis.
UNIVERSITY OF ST. ANDREWS
4 P.M. (Department of Medicine, Dundee.) Mr. R. D. Muckart: Postur

Thursday, 5th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M. Dr. Southwood: Aspects of Preventive Cardiology—2. The Rise Biochemistry. (Last of two Milroy lectures.)
ROYAL COLLEGE OF SURGEONS OF ENGLAND
3.45 P.M. Dr. R. McP. Livingston: Human Embryo, the Developme and Form. (Arnott demonstration.)
5.30 P.M. Mr. Victor Riddell: Thyroid Gland and Recurrent Laryng Nerve. (Otolaryngology lecture.)
UNIVERSITY COLLEGE
5 P.M. Prof. F. G. Young: Hormones and Metabolic Processes— Anterior Pituitary Hormones. (Last of three lectures.)
ROYAL SOCIETY OF MEDICINE
8 P.M. *Neurology.* Dr. Frank Elliott, Dr. John Marshall, Prof. Charl Rob: Cerebrovascular Disease.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. A. Rogers: Human Physiology in Antarctica.
WEST OF ENGLAND CHILD HEALTH GROUP
5.30 P.M. (Children's Hospital, Bristol.) Mr. David Stevens: Catarrh Deafness in Childhood.
LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool, 3
8 P.M. Dr. T. R. Littler: Rheumatoid Arthritis. Dr. Heinz Fuld: U of Chloroquin in Rheumatoid Arthritis.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology Department, Dundee.) Dr. J. C. Hoyle: Recent Wo on Sarcoidosis.

Friday, 6th

UNIVERSITY OF LONDON
5.15 P.M. (Westminster Medical School, Horseferry Road, S.W.1 Prof. L. T. Samuels (U.S.A.): Studies of Steroid Biosynthesis Testicular Interstitial Cells.
ROYAL SOCIETY OF MEDICINE
2.30 P.M. *Laryngology.* Mr. J. I. Munro Black, Mr. H. J. Shaw: Bl Dissection of the Neck.
5.30 P.M. *Anæsthetics.* Dr. A. Crampton Smith, Dr. J. M. K. Spaldi Intermittent Pressure Respiration. Some Physiolog Observations.
POSTGRADUATE MEDICAL SCHOOL
10 A.M. Mr. B. N. Brooke: Certain Aspects in the Care and Treatment Ulcerative Colitis.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Mr. K. G. Rotter: Otitis Externa.
ROYAL MEDICO-CHIRURGICAL SOCIETY OF GLASGOW, 242, St. Vinc Street, C.2
8.30 P.M. Dr. J. M. Lenihan: Radiation and Life.

Saturday, 7th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
11.30 A.M. Dr. J. J. Groen (Utrecht): The Basis of Vestibu Examination.
MIDLAND THORACIC SOCIETY
3 P.M. (36, Harborne Road, Edgbaston, Birmingham, 15.) Mr. O. Tubbs: Abnormalities of the Diaphragm.